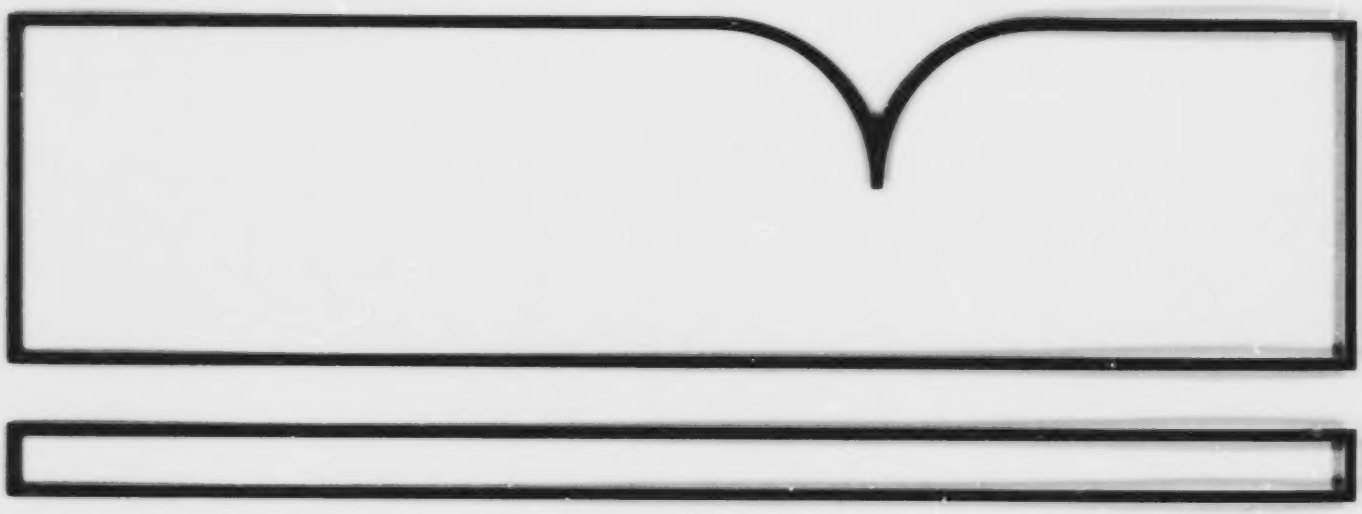
PB88-243845

Health and Environmental Effects Profile for Methyl Chloride

(U.S.) Environmental Protection Agency
Cincinnati, OH

Jun 86



U.S. Department of Commerce
National Technical Information Service
NTIS

TECHNICAL REPORT DATA (Please read Instructions on the reverse before completing)		
1. REPORT NO. EPA/600/X-86/156	2.	3. RECIPIENT'S ACCESSION NO. PB88 243845/AS
4. TITLE AND SUBTITLE Health and Environmental Effects Profile for Methyl Chloride		5. REPORT DATE June 1986
		6. PERFORMING ORGANIZATION CODE
7. AUTHOR(S)		8. PERFORMING ORGANIZATION REPORT NO
9. PERFORMING ORGANIZATION NAME AND ADDRESS		10. PROGRAM ELEMENT NO.
		11. CONTRACT/GRANT NO
12. SPONSORING AGENCY NAME AND ADDRESS Environmental Criteria and Assessment Office Office of Research and Development U.S. Environmental Protection Agency Cincinnati, OH 45268		13. TYPE OF REPORT AND PERIOD COVERED
		14. SPONSORING AGENCY CODE EPA/600/22
15. SUPPLEMENTARY NOTES		

16. ABSTRACT

The Health and Environmental Effects Profile for Methyl Chloride was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Methyl chloride has been evaluated as a carcinogen. The human carcinogen potency factor (q_1^*) for methyl chloride is 1.26×10^{-2} $(mg/kg/day)^{-1}$ for oral exposure.

The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. The RQ value for methyl chloride is 1000.

17. KEY WORDS AND DOCUMENT ANALYSIS		
a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field Group

18. DISTRIBUTION STATEMENT Public	19. SECURITY CLASS (This Report) Unclassified	21. NO. OF PAGES 110
	20. SECURITY CLASS (This page) Unclassified	22. PRICE

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

PB88-243845

EPA/600/X-86/156
June 1986

HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR METHYL CHLORIDE

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
OFFICE OF RESEARCH AND DEVELOPMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY
CINCINNATI, OH 45268

REPRODUCED BY
NATIONAL TECHNICAL
INFORMATION SERVICE
U.S. DEPARTMENT OF COMMERCE
SPRINGFIELD, VA 22161

DISCLAIMER

This document has been reviewed in accordance with U.S. Environmental Protection Agency policy and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste and Emergency Response by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA), as well as to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched." The literature search material is current through November, 1985.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Reference doses (RfDs) for chronic exposures. An RfD is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, RfDs are not estimated in this document series. Instead, a carcinogenic potency factor of q_1^* (U.S. EPA, 1980) is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA. These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity and acute mammalian toxicity).

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA and CERCLA dockets.

ACKNOWLEDGEMENTS

The initial draft of this report was prepared by Syracuse Research Corporation under Contract No. 68-03-3228 for U.S. EPA's Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. Dr. Christopher DeRosa was the Technical Project Monitor and Helen Ball was the Project Officer. The final documents in this series were prepared for the Office of Solid Waste, Washington, DC.

Scientists from the following U.S. EPA offices provided review comments for this document series:

Environmental Criteria and Assessment Office, Cincinnati, OH
Carcinogen Assessment Group
Exposure Assessment Group
Reproductive Effects Assessment Group

Editorial review for the document series was provided by:
Judith Olsen and Erma Durden
Environmental Criteria and Assessment Office, Cincinnati, OH

Technical support services for this document series were provided by:
Bette Zwayer, Pat Daunt, Karen Mann, and Jacky Bohanon
Environmental Criteria and Assessment Office, Cincinnati, OH.

EXECUTIVE SUMMARY

Methyl chloride is a colorless gas with an ethereal odor at room temperature and atmospheric pressure. It is soluble in most organic solvents but is sparingly soluble in water. Methyl chloride is stable both in the gas and liquid form. It decomposes in open flames to yield hydrogen chloride, carbon dioxide, and small amounts of carbon monoxide and phosgene (Ahlstrom and Steele, 1979). In neutral water, methyl chloride slowly hydrolyzes to form methanol and hydrogen chloride (U.S. EPA, 1980a).

In recent years, methyl chloride has been manufactured in the United States by seven companies at eight locations (SRI, 1985; USITC, 1985; CMR, 1983). The 1984 U.S. production volume of this chemical was 482.5 million pounds (USITC, 1985). The two principal processes used for the industrial production of methyl chloride are chlorination of methane and hydrochlorination of methanol; >98% of the methyl chloride produced in the United States is through the latter process. About 60% of the annual production of methyl chloride is used in the manufacture of silicones and ~15% in the production of tetramethyl lead (CMR, 1983). The use of methyl chloride in refrigeration devices has been almost completely phased out in favor of other substances (U.S. EPA, 1980b).

The sources of atmospheric methyl chloride are both natural and anthropogenic. The most important natural source of methyl chloride in the atmosphere is seawater. Combustion of both natural and man-made materials, such as burning of agricultural field residues, controlled burning of forest fires, wildfires, burning of PVC waste and building fires, contribute significantly to atmospheric methyl chloride (Lovelock, 1975; Crutzen et al., 1978; Palmer, 1976). The contribution of industrial sources to the

global methyl chloride burden is very small. It has been estimated that ~0.018 million tons/year of methyl chloride is through its industrial production compared with its total emission of 5.6 million tons/year from other natural and nonindustrial sources.

Methyl chloride is reasonably stable in the atmosphere. Reaction with OH• is the most significant process for the removal of methyl chloride from the troposphere. The average tropospheric lifetime of methyl chloride therefore is estimated to be 1.1 years. About 2% of tropospheric methyl chloride is expected to be transferred to the stratosphere, where it may participate in the destruction of the ozone layer. Of the total chlorine in the stratosphere originating from halocarbons, ~20-25% is currently contributed by methyl chloride (Crutzen and Gidel, 1983; Edwards et al., 1982).

Compared with its loss through evaporation, the loss of methyl chloride from aquatic media through photolysis, oxidation or biodegradation is insignificant. The half-life of evaporation of methyl chloride from aquatic media is ~2-3 hours (Lyman et al., 1982). Pertinent experimental data regarding the sorption coefficient of methyl chloride in sediments or bioaccumulation factors in aquatic organisms were not located in the available literature cited in the Appendix. Values estimated from correlation equations (Lyman et al., 1982) suggest that neither of these processes are significant in aquatic media.

In the absence of experimental data, the fate of methyl chloride in soil has been speculated from its fate in aquatic media. Evaporation is likely to be the most important loss process from soil. Biodegradation in soil may be significant, but no quantitative half-life value can be estimated. Leaching of methyl chloride from soil to groundwater, although not generally likely, may occur from dumpsites.

Methyl chloride is always present in the atmosphere at low concentrations, dependent upon seasonal, diurnal and latritudinal variations (Khalil and Rasmussen, 1981; Lioy et al., 1983; Singh et al., 1982). The average levels of methyl chloride are 980 ppt in U.S. urban areas, 610 ppt in continental background, and 1200 ppt in marine background. The concentrations of methyl chloride in indoor air can be higher than outdoor atmosphere (NAS, 1978). A concentration as high as 20,000 ppt has been reported inside an apartment after a cigarette was smoked (NAS, 1978), but exposure from certain occupational settings is likely to present the greatest health risks (U.S. EPA, 1980b). The average intake of methyl chloride from inhalation of atmospheric methyl chloride has been estimated to be 41 µg for United States urban/suburban areas and 25 µg for U.S. rural areas.

Methyl chloride has been detected in a few drinking waters in the United States and Canada, though the concentrations in most cases are below the detection limit, preventing quantification of the results. Methyl chloride was detected at a concentration of <5 µg/ℓ in ~3% of drinking water samples analyzed by Otson et al. (1982). Its concentration in a drinking water well in Massachusetts was reported to be 44 µg/ℓ (Burmaster, 1982). The majority of individuals in the United States will experience no intake of methyl chloride from drinking water. Methyl chloride has not been reported in any foods; therefore, it is not possible to estimate its intake from food sources.

There is little information concerning the toxicity of methyl chloride to aquatic organisms. LC_{50} values of 550 mg/ℓ and 270 mg/ℓ were reported for bluegills and tidewater silversides, respectively (Dawson et al., 1978). Toxicity thresholds for algae and bacteria are in the range of 500-1450 mg/ℓ (Bringmann and Kuehn, 1976, 1980).

Pertinent data regarding the absorption of methyl chloride from the gastrointestinal tract could not be located in the available literature as cited in the Appendix. Following inhalation exposure of rats, dogs and humans, methyl chloride was rapidly absorbed from the lungs with steady-state blood and expired air levels reached within 1 hour during exposure (Putz-Anderson et al., 1981a,b; Nolan et al., 1985; Landry et al., 1983a). The blood and expired air levels remained at steady-state until exposure was terminated and then declined rapidly in a biphasic manner. Using 2-compartment pharmacokinetic models, Nolan et al. (1985) calculated that humans exposed to 10 or 50 ppm (20.7 or 103 mg/m^3) absorbed 1.4-3.7 µg methyl chloride/min/kg while Landry et al. (1983a) calculated uptakes 0.20 nmol/min/g (0.01 mg/min/kg) and 3.27 nmol/min/g (0.165 ng/min/kg) in rats exposed to 50 and 1000 ppm (103 and 2065 mg/m^3), respectively.

Following absorption, methyl chloride is rapidly and extensively distributed to organs and tissues (U.S. EPA, 1980b). At 2 days following inhalation exposure of rats to ^{14}C-methyl chloride, radioactivity was still detected in the tissues and carcasses of rats; the persistence of radioactivity was due to incorporation of the radioactive carbon atom into macromolecules by normal anabolic processes, rather than to direct binding of ^{14}C-methyl chloride to the macromolecules (Kornbrust et al., 1982). Bus et al. (1982) demonstrated the transplacental transfer of methyl chloride in rats.

Methyl chloride is extensively metabolized. Metabolism appears to involve reaction of methyl chloride with glutathione and cysteine to yield S-methyl glutathione and S-methyl cysteine and other sulfur-containing metabolites (Redford-Ellis and Gowenlock, 1971a,b; Landry et al., 1983a; Dodd et al., 1982) that can be excreted in the urine (Landry et al., 1983a;

Van Doorn et al., 1980). Subsequent metabolism of S-methylcysteine may lead to cytochrome P-450 dependent metabolism of methanethiol to formaldehyde and formic acid, whose carbon atoms enter the one-carbon pool for incorporation into macromolecules or formation of CO_2 (Kornbrust and Bus, 1983). Methyl chloride may also be metabolized directly to formaldehyde, which in turn is oxidized to formic acid.

Very little unchanged methyl chloride is excreted in expired air, urine or bile (Sperling et al., 1950). Blood and expired air levels of methyl chloride declined rapidly when inhalation exposure of rats, dogs or humans ceased (Landry et al., 1983b; Nolan et al., 1985). The elimination was biphasic; half-lives for the B-phase were 15 minutes in rats, 40 minutes in dogs and 50-90 minutes in humans. The pharmacokinetics of radioactivity derived from ^{14}C-methyl chloride are markedly different (Landry et al., 1983b; Bus, n.d.). Blood levels of radioactivity in rats did not reach steady state during inhalation exposure, but remained constant for 4 hours following exposure and then declined in a biphasic manner with a B-phase half-life of 17.6 hours (Bus, n.d.). Extensive metabolism of ^{14}C-methyl chloride may have led to a temporary accumulation of metabolites in tissues, accounting for the lag in elimination. Excretion of radioactivity following 6-hours inhalation exposure of rats was essentially complete in 18 hours; 63.9, 32 and 3.9% of the total excreted radioactivity were excreted in the expired air, urine and feces, respectively (Bus, 1978).

Inhalation exposure of mice to methyl chloride at 0, 50, 225 or 1000 ppm (0, 103, 465 or 2065 mg/m^3), 6 hours/day, 5 days/week for 2 years resulted in a statistically significant increased incidence of benign and malignant kidney tumors in the high dose male mice compared with controls (Pavkov et al., 1981; CIIT, 1983; NIOSH, 1984). No carcinogenic effect was observed in

female mice or male and female rats similarly treated. Methyl chloride was positive for reverse mutations in Salmonella typhimurium strains TA100 and TA1535 with and without metabolic activation (Andrews et al., 1976; Simmon et al., 1977), for forward mutation in S. typhimurium TM677 and human lymphoblasts, for SCE in human lymphoblasts (Fostel et al., 1985) and for dominant lethal mutations in male rats (Working et al., 1985a,b). Methyl chloride was teratogenic to the offspring of mice exposed by inhalation to 500 or 750 ppm (1033 or 1549 mg/m^3), 6 hours/day during gestation, resulting in increased incidences of dead and malformed fetuses and heart defects (Wolkowski-Tyl et al., 1983a,b). Exposure levels $\geq$750 ppm were toxic to dams. No effects were observed at $\leq$250 ppm, 6 hours/day. No teratogenic effects were observed in the offspring of rats exposed to 100, 500 or 1500 ppm (207, 1033 or 3098 mg/m^3) 6 hours/day during gestation; however, maternal toxicity (reduced body weight gain) and fetotoxicity (reduced fetal body weight, reduced crown-rump length and delayed ossification) were observed at 1500 ppm (Wolkowski-Tyl et al., 1983b). Short-term inhalation exposure (5-9 days) of male rats to $\geq$2000 ppm (4130 mg/m^3), 6 hours/day resulted in testicular degeneration, epididymal granuloma, abnormal sperm and reduced fertility (Morgan et al., 1982; Chapin et al., 1984; Working et al., 1985a,b). No effects on reproductive function or testicular morphology were observed at 1000 ppm, 6 hours/day (Working et al., 1985b). In a 2-generation study, male rats exposed to 1500 ppm (3098 mg/m^3), 6 hours/day for 5-7 days/week for 10-12 weeks and mated to exposed or unexposed females were infertile, while males exposed to 475 ppm (981 mg/m^3) had reduced fertility (Hamm et al., 1985). The infertility was found to be partially reversible. Treatment-related histopathological lesions in the testis and epididymis were found only in 1500 ppm F_0 males. No adverse effects were observed in the F_1 generation.

In a 2-year inhalation study, male and female rats and mice were exposed to methyl chloride at 0, 50, 225 or 1000 ppm (0, 103, 465 or 2065 mg/m^3) 6 hours/day, 5 days/week for up to 2 years (Pavkov et al., 1980, 1981; CIIT, 1983; NIOSH, 1984). Effects in male rats that were considered to be treatment-related were significantly decreased relative liver weights at 50 ppm at 24 months, increased relative kidney weights at 50 and 225 ppm at the 6-month kill, decreased relative testes weight at 1000 ppm at 24 months, decreased body weight gain and atrophy and degeneration of the seminiferous tubules. The only effects in female rats were decreased body weight gain and decreased relative kidney weights at 24 months in the 1000 ppm group. In mice, no effects were observed at 50 ppm, while the only effect at 225 ppm was increased relative heart weights of females at 24 months. At 1000 ppm, males and females had increased mortality and neurofunctional impairment. Males had increased levels of SGPT and males and females had liver lesions consisting of centrilobular necrosis, karyomegaly, cytomegaly and vacuolar degeneration. Other treatment-related lesions at 1000 ppm included hyperplasia and karyomegaly of the renal epithelium and degeneration of seminiferous tubules in males and degeneration of the cerebellar granular layer in males and females.

Inhalation exposure to $\geq$500 ppm ($\geq$1032 mg/m^3), 6 hours/day, 6 days/week were fatal to rabbits, guinea pigs, mice, dogs, monkeys and cats, with the first deaths occurring between 1 and 211 days (Smith and von Oettingen, 1947a,b). No rats died at 500 ppm, while all species tested survived 300 ppm (620 mg/m^3), 6 hours/day, 6 days/week for 64 weeks. Exposures $\geq$500 ppm were associated with severe neuromuscular impairment. In a 13-week study, rats exposed to $\geq$750 ppm (1549 mg/m^3) 6 hours/day, 5 days/week had

decreased body weight gain (Mitchell et al., 1979). Rats and mice exposed to 1500 ppm (3098 mg/m³) had increased liver weights and increased incidences of vacuolization of hepatocytes.

Occupational exposure to an average airborn concentration of 33.57 ppm (69.3 mg/m³) has been associated with impaired performance of time-sharing tasks and increased magnitudes of finger tremors (Repko et al., 1976).

A q_1^* for humans of 1.26×10^{-2} $(mg/kg/day)^{-1}$ and a human potency factor (F) of 9.56×10^{-2} $(mg/kg/day)^{-1}$ was derived from the data for increased incidence of kidney tumors in mice in the 2-year inhalation study by CIIT (1983). Methyl chloride is classified as a possible human carcinogen based on limited positive animal data (one species and sex) and positive genotoxic data, thus a Group C and a Potency Group 4 classification is considered most appropriate; therefore, methyl chloride would have a LOW hazard ranking under CERCLA. An RQ of 1000 for chronic toxicity was based on the data for reduced fertility of rats in the study by Hamm et al. (1985).

TABLE OF CONTENTS

		Page
1.	INTRODUCTION	1
1.1.	STRUCTURE AND CAS NUMBER	1
1.2.	PHYSICAL AND CHEMICAL PROPERTIES	1
1.3.	PRODUCTION DATA	2
1.4.	USE DATA	4
1.5.	SUMMARY	4
2.	ENVIRONMENTAL FATE AND TRANSPORT PROCESSES	5
2.1.	AIR	5
2.2.	WATER	9
2.3.	SOIL	11
2.4.	SUMMARY	12
3.	EXPOSURE	14
3.1.	AIR	14
3.2.	WATER	17
3.3.	FOOD	20
3.4.	SUMMARY	20
4.	PHARMACOKINETCS	22
4.1.	ABSORPTION	22
4.2.	DISTRIBUTION	23
4.3.	METABOLISM	25
4.4.	EXCRETION	27
4.5.	SUMMARY	30
5.	EFFECTS	32
5.1.	CARCINOGENICITY	32
5.2.	MUTAGENICITY	33
5.3.	TERATOGENICITY	37
5.4.	REPRODUCTIVE EFFECTS	38
5.5.	CHRONIC AND SUBCHRONIC TOXICITY	42
5.6.	OTHER RELEVANT INFORMATION	47
5.7.	SUMMARY	48
6.	AQUATIC TOXICITY	51
6.1.	ACUTE	51
6.2.	CHRONIC	51
6.3.	PLANTS	51
6.4.	RESIDUES	51
6.5.	SUMMARY	52

TABLE OF CONTENTS (cont.)

		Page
7.	EXISTING GUIDELINES AND STANDARDS	53
	7.1. HUMAN	53
	7.2. AQUATIC	53
8.	RISK ASSESSMENT	54
9.	REPORTABLE QUANTITIES	60
	9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY	60
	9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY	66
10.	REFERENCES	71
APPENDIX:	LITERATURE SEARCHED	90

LIST OF TABLES

No.	Title	Page
2-1	Rate Constant for the Reaction of OH• with Methyl Chloride.	7
3-1	Recent Methyl Chloride Levels in the United States Urban Areas, in Continental Background, and Other Areas of the World	15
3-2	Concentrations of Methyl Chloride in Various Indoor Atmospheres	18
5-1	Numbers of Male Mice Sacrificed or Dying and Kidney Tumor Prevalence in Each Month From the 12th Month Onward	34
5-2	Incidence of Benign or Malignant Kidney Tumors in Male B6C3F1 Mice Exposed by Inhalation to Methyl Chloride (99.99% Pure) for up to 24 Months	35
5-3	Mutagenicity Testing of Methyl Chloride	36
8-1	Cancer Data Sheet for Derivation of q_1^*	57
8-2	Cancer Data Sheet for Derivation of q_1^*	59
9-1	Inhalation Toxicity Summary for Methyl Chloride	61
9-2	Inhalation Composite Scores for Methyl Chloride	64
9-3	Methyl Chloride: Minimum Effective Dose (MED) and Reportable Quantity (RQ).	67
9-4	Derivation of Potency Factor (F) for Methyl Chloride.	69

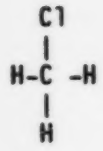
LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
BCF	Bioconcentration factor
CNS	Central nervous system
CS	Composite score
dpm	Disintegrations per minute
DNA	Deoxyribonucleic acid
EEG	Electroencephalogram
K_{oc}	Soil sorption coefficient
K_{ow}	Octanol/water partition coefficient
LC_{50}	Concentration lethal to 50% of recipients (and all other subscripted dose levels)
MED	Minimum effective dose
NADPH	Nicotinamide adenine dinucleotide phosphate (reduced form)
NPSH	Nonprotein sulfhydryl
ppm	Parts per million
ppt	Parts per trillion
PVC	Polyvinyl chloride
RV_d	Dose-rating value
RV_e	Effect-rating value
RNA	Ribonucleic acid
RQ	Reportable quantity
SCE	Sister-chromatid exchange
SGPT	Serum glutamic pyruvic transaminase
STEL	Short-term exposed limit
TLV	Threshold limit value
TWA	Time-weighted average

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

The structure, empirical formula and molecular weight for methyl chloride, also known as chloromethane and monochloromethane, is as follows:



Empirical formula: CH_3Cl

Molecular weight: 50.49

CAS Registry number: 74-87-3

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Methyl chloride at room temperature and atmospheric pressure is a colorless gas with an ethereal odor and sweet taste. It is commercially handled as a liquid. Methyl chloride is soluble in most organic solvents (Ahlstrom and Steele, 1979). The relevant physical properties of methyl chloride are given below:

Melting point:	-97.7°C	Weast, 1980
Boiling point at 1 atm:	-24.2°C	Weast, 1980
Density $\frac{20}{4}$ (g/cm³):	0.916	Weast, 1980
Flash point (open cup):	<0°C	Ahlstrom and Steele, 1979
Flammability limits in air, vol %:	10.7-17.4	Ahlstrom and Steele, 1979
Vapor pressure (mm Hg) at 20°C:	3670	Ahlstrom and Steele, 1979
	3756	Pearson and McConnell, 1975
	2620	Gallant, 1966
Solubility in water at 20°C:	6263 mg/ℓ	Horvath, 1982
	7250 mg/ℓ	Pearson and McConnell, 1975
	7400 mg/ℓ	Neely, 1976

Henry's Law Constant at 20°C (atm m^3 mol^{-1}):	$7.3x10^{-3}$ (expected) $8.8x10^{-3}$ (estimated)	Pearson and McConnell, 1975 Neely, 1976
Log K_{ow}:	0.91	Hansch and Leo, 1979

Dry methyl chloride is stable both in the gas and liquid form. In the presence of moisture, the liquid form slowly decomposes and becomes corrosive to metals. Thermal decomposition of methyl chloride in the absence of air is virtually complete at 1400°C. It decomposes in an open flame to give hydrogen chloride, carbon dioxide, and small amounts of carbon monoxide and phosgene. Methyl chloride reacts with ammonia in the vapor phase to form amines. It is hydrolyzed by boiling sodium hydroxide solution (Ahlstrom and Steele, 1979). In water at pH 7 (neutral), methyl chloride slowly hydrolyzes to form methanol and hydrogen chloride. In seawater, iodomethane can react with chloride ion to yield methyl chloride (U.S. EPA, 1980a). This reaction is the major source of atmospheric methyl chloride.

1.3. PRODUCTION DATA

According to TSCA Inventory of Chemical Producers, 10 U.S. producers in 12 sites manufactured 100-500 million pounds of methyl chloride in 1977 (U.S. EPA, 1980b). According to SRI (1985), the following six producers, with their annual capacities stated, manufactured methyl chloride in the United States as of January, 1985:

Company and Location	Annual Capacity (millions of pounds)
Diamond Shamrock Corp. Belle, WV	25
Dow Chemical U.S.A. Plaquemine, LA	150
Dow Corning Corp. Carrollton, KY Midland, MI	100

General Electric Co. Waterford, NY	65
LCP Chemicals and Plastics, Inc. Moundsville, WV	22
Vista Chemical Co. Lake Charles, LA	100
Total	462

USITC (1985) also lists Ethyl Corp. (Baton Rouge and Louisville) as a producer. The total production volume of methyl chloride in the U.S. in 1984 was 482.5 million pounds (USITC, 1985) and, since only insignificant quantities are either imported or exported, it is estimated that Ethyl Corp. in Baton Rouge must have produced >20 million pounds in 1984. According to U.S. EPA's TSCA Inventory (U.S. EPA, 1977), in 1977 Ethyl Corp. produced 60-150 million pounds of methyl chloride, and according to CMR (1983), Ethyl Corp. (Baton Rouge) produced 100 million pounds of methyl chloride in 1983.

The two principal processes used for the industrial production of methyl chloride are chlorination of methane and the reaction of hydrogen chloride and methanol, which produces methyl chloride as the sole product. Chlorination of methane yields several chlorohydrocarbons including methyl chloride (Ahlstrom and Steele, 1979). Over 98% of methyl chloride produced in the United States is made by the hydrochlorination of methanol (U.S. EPA, 1980b; SRI, 1985). The two grades of methyl chloride available commercially are the refrigerant and the technical. The refrigerant grade is very pure to prevent destruction of the refrigeration equipment by impurities and generally contains <75 ppm water. A typical technical grade methyl chloride contains the following impurities (ppm): water, 100; acid (as HCl), 10; methyl ether, 20; methanol, 50; acetone, 50; vinyl chloride, 100; ethyl chloride, 100; nonvolatile residue, 100 (Ahlstrom and Steele, 1979).

1.4. USE DATA

The recent use pattern for methyl chloride in the United States is as follows: intermediate in the manufacture of silicones, 60%; production of tetramethyl lead, 15%; methyl cellulose production, 6%; production of herbicides, 4%; quarternary amines production, 4%; butyl rubber production, 3%; miscellaneous, 3%; exports, 5% (CMR, 1983). Although some refrigeration devices using methyl chloride are still in operation today, this use has been almost completely phased out in favor of other refrigerants (U.S. EPA, 1980b).

1.5. SUMMARY

Methyl chloride is a colorless gas with an ethereal odor at room temperature and atmospheric pressure. It is soluble in most organic solvents but is sparingly soluble in water. Dry methyl chloride is stable both in the gas and liquid form. It decomposes in open flames to yield hydrogen chloride, carbon dioxide, and small amounts of carbon monoxide and phosgene (Ahlstrom and Steele, 1979). In neutral water, methyl chloride slowly hydrolyzes to form methanol and hydrogen chloride (U.S. EPA, 1980a).

In recent years, methyl chloride has been manufactured in the United States by seven companies at eight locations (SRI, 1985; USITC, 1985; CMR, 1983). The 1984 U.S. production volume of this chemical was 482.5 million pounds (USITC, 1985). The two principal processes used for the industrial production of methyl chloride are chlorination of methane and hydrochlorination of methanol, and over 98% of the methyl chloride produced in the United States is through the latter process. About 60% of the annual production of methyl chloride is used in the manufacture of silicones and ~15% in the production of tetramethyl lead (CMR, 1983). The use of methyl chloride in refrigeration devices has been almost completely phased out in favor of other substances (U.S. EPA, 1980b).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. AIR

The sources of atmospheric methyl chloride are both natural and anthropogenic. The most significant source of atmospheric methyl chloride is likely to be seawater (Lovelock, 1975; Crutzen et al., 1978). Combustion sources of both natural and manmade origin contributes significantly to atmospheric methyl chloride. It has been estimated by Palmer (1976) that burning agricultural field residues, controlled burning of forest residues and wildfires in the United States alone contribute ~2700, 83,200, 43,500 tons/year to atmospheric methyl chloride, respectively. Combustion sources of manmade origin, such as burning of PVC waste and building fires, contributed another 80,600 tons to atmospheric methyl chloride in 1974 (Palmer, 1976). The importance of combustion sources in contributing to the atmospheric methyl chloride burden has been shown by other authors (Edgerton et al., 1984; Rasmussen et al., 1980). Rasmussen et al. (1980) estimated that ~12-20% of the total global emission of methyl chloride (2.5-5 million tons/year) is due to biomass burning. The contribution of industrial sources to the global methyl chloride burden is very small. Edwards et al. (1982) estimated that ~0.018 million tons/year of methyl chloride is globally emitted through industrial production compared with its total emission of 5.6 million tons/year from other natural and nonindustrial sources. Such nonindustrial sources are biomass burning, including residue burning from agricultural fields and forests. Thus, industrial production of methyl chloride constitutes ~0.3% of the total atmospheric burden of methyl chloride.

The atmospheric fate of methyl chloride is reasonably well-studied. Of the several likely processes that are responsible for the loss of atmospheric methyl chloride, reaction with OH• is most important. The rate values of this reaction are given in Table 2-1.

It is possible to determine the tropospheric lifetime of methyl chloride from the rate constant of its reaction with OH•, provided the tropospheric concentration of the OH• is known. The concentration of OH• in the troposphere is subject to seasonal, altitudinal and latitudinal variation (Yung et al., 1975; Derwent and Eggleton (1978). In addition, hemispheric (northern and southern) difference also alters the concentration of tropospheric OH• (Crutzen and Gidel, 1983). Therefore, a globally-averaged value for tropospheric OH• is used for estimating the lifetime of a chemical in the troposphere that is due to its reaction with OH•. Earlier measurements by several investigators, based on northern/southern hemisphere CH_3CCl_3 measurements, put the mean OH• value between 2.5×10^5 and 1×10^6 radicals cm^{-3} (Logan et al., 1981). More recent measurements, however, show that this average OH• concentration is an underestimate and indicate that a mean value for the concentration of OH• in the northern hemisphere would be 1×10^6 radicals cm^{-3} (Davis et al., 1982; Logan et al., 1981; Crutzen and Gidel, 1983).

Assuming that the reaction of trophospheric methyl chloride with OH• is the most significant reaction, the lifetime of this chemical in the troposphere can be estimated from the equation $\tau = 1 \div K_2 \times [OH]$, where τ is the lifetime, K_2 is the rate constant for the second-order reaction and [OH] is the average tropospheric concentration for the OH•. Depending on the values for K_2 and [OH] or the model used, the tropospheric lifetime for methyl chloride has been variously estimated to be

TABLE 2-1

Rate Constant for the Reaction of OH· with Methyl Chloride

Rate Constant ($\times 10^{14}$ cm^3 $molecule^{-1}$ sec^{-1})	Temperature (°K)	Reference
3.6±0.8	296	Howard and Everson, 1976
4.4±0.5	298	Perry et al., 1976
8.5	298	Cox et al., 1976
4.29±0.21	298	Davis et al., 1976
3.1±0.8	302.5	Butler et al., 1978
4.10±0.68	297	Paraskevopoulos et al., 1982
3.95±0.26	293	Jeong and Kaufman, 1982

0.2-3 years (Derwent and Eggleton, 1978; Singh et al., 1981; Edwards et al., 1982; Perry et al., 1976; Cox et al., 1976; Davis et al., 1976; Yung et al., 1975). A reasonable estimate of tropospheric lifetime for methyl chloride can be based on the more recent average value of OH· concentration at 10^6 radicals cm^{-3}, and the reaction rate constant K_2 of 3×10^{-14} cm^3 $molecule^{-1}$ sec^{-1} (Davis et al., 1976) at an average tropospheric temperature of 265°K (Davis et al., 1976; Edwards et al., 1982). With these values, the lifetime of tropospheric methyl chloride is ~1.1 years.

The direct photochemical reaction of methyl chloride in the atmosphere is not likely to be significant. The absorption cross-section for atmospheric methyl chloride is $<2 \times 10^{-24}$ cm^2 $molecule^{-1}$ (Crutzen et al., 1978), which is considered to be low. Robbins (1976) showed that the photoreaction of methyl chloride in the troposphere is not a significant fate process. The rate constant for the reaction of O_3 with methyl chloride was reported by Herron and Huie (1973) and Barassin and Combourieu (1974) as 1.2×10^{-16} and 3.8×10^{-16} cm^3 $molecule^{-1}$ sec^{-1}, respectively. Assuming a concentration of 2.5×10^4 molecule cm^{-3} for atmospheric atomic oxygen, it is concluded that this reaction will not play a significant role in the removal of methyl chloride from the atmosphere. The reaction of chlorine atoms with atmospheric methyl chloride was studied by Spence et al. (1976), who concluded that this reaction will not be significant in the atmosphere because the chlorine atoms will react much faster with such atmospheric species as ozone and methane before reacting with methyl chloride. Sanhueza and Heicklen (1975) reported the rate constant for Cl atom reaction with methyl chloride at 32°C as 6×10^{-11} cm^3 $molecule^{-1}$ sec^{-1}. The experiment was performed, however, at much higher concentrations of both methyl chloride and chlorine than are expected in the atmos-

phere and at a higher reaction temperature. Therefore, the reported rate constant has not been used for deriving the lifetime of methyl chloride because of its reaction with chlorine atoms under atmospheric conditions.

The removal of atmospheric methyl chloride through washout/rainout or dry deposition has not been comprehensively studied. Davis et al. (1982), however, reported these removal mechanisms as insignificant, compared with its removal through OH• reaction.

If the lifetime of tropospheric methyl chloride is assumed to be 1.1 years and the turnover time for the tropospheric to stratospheric transfer is 30 years (Dilling, 1982), ~2% of tropospheric methyl chloride will be transferred to the stratosphere. About 99.7% of the stratospheric methyl chloride, however, would originate from natural and nonindustrial sources (Edwards et al., 1982). Of the total chlorine in the stratosphere originating from halocarbons, ~20-25% currently comes from methyl chloride (Crutzen and Gidel, 1983; Edwards et al., 1982).

2.2. WATER

The photolytic fate of methyl chloride in aquatic media has not been studied comprehensively. Based on its low absorption cross-section in the gas phase at wavelengths >290 nm (see Section 2.1.), significant photodegradation of methyl chloride in aquatic media does not seem likely. Dilling et al. (1975) studied the decomposition rate of dichloromethane, a compound structurally similar to methyl chloride, in aqueous solution. At a concentration of 1 ppm in aerated sealed tubes, no significant difference between the decomposition rates of dichloromethane in tubes exposed to sunlight vs. dark was observed over periods of 6-12 months. Therefore, photolysis of methyl chloride solution by natural sunlight is also expected to be insignificant.

Information on the rate of oxidation of methyl chloride by oxygen or other free radicals ($HO_2\cdot$, OH·, etc.) could not be located in the available literature. On the basis of oxidation probability of structurally similar compounds, Callahan et al. (1979) concluded that oxidation may not be a significant fate process for aquatic methyl chloride.

Heppolette and Robertson (1966) studied the hydrolysis of methyl chloride in neutral aqueous solution. At 50°C, the hydrolysis rate constant was given as 7.6×10^{-7} sec^{-1}. At 25°C, the same rate constant is 2.37×10^{-8} sec^{-1} (Mabey and Mill, 1978), corresponding to a half-life of 0.93 years. The hydrolysis rate was found to be independent of pH at pH<10 (Mabey and Mill, 1978). Estimation by other investigators put this half-life value at 2.5 years (Callahan et al., 1979). Therefore, hydrolysis is not a significant reaction for aquatic methyl chloride.

The biodegradation of methyl chloride with isolated methylotrophic microorganisms was reported by several investigators (Haber et al., 1983; Knackmuss, 1980). These microorganisms oxidized methyl chloride to formaldehyde. Such studies, however, are difficult to correlate with the biodegradation of compounds in natural systems. The microbial degradation rate constant for methyl chloride in natural aquatic medium is estimated as 3×10^{-9} $m\ell\ cell^{-1}\ hour^{-1}$ (Jaber et al., 1984). Assuming the concentration of microorganisms in natural water that are capable of degrading methyl chloride as 5×10^{5} cell $m\ell^{-1}$ (Oduntan and Odeyemi, 1984; Banerjee et al., 1984), the biodegradation half-life is estimated as ~19 days. Therefore, biodegradation is also not a significant aquatic degradation process for methyl chloride.

The volatilization of methyl chloride from aqueous solution was both experimentally and theoretically estimated in several publications (Dilling,

1977; Dilling et al., 1975; Neely, 1976). The evaporative half-life for methyl chloride was experimentally determined to be ~28 minutes from a 1 ppm solution at 25°C under 200 rpm stirring in still air (<0.2 mph air current) and an average solution depth of 6.5 cm. The theoretical calculations based on interphase transfer processes yield a half-life value of ~15 minutes. A more realistic calculation based on a windspeed of 3 M/second, current speed of 1 M/second and depth of 1 M provided an estimated half-life of 2.4 hours (Lyman et al., 1982). Therefore, evaporation from aquatic media is the most important removal mechanism for aquatic methyl chloride. Pertinent data on the sorption of methyl chloride into suspended particulate and sediments in aquatic media could not be located in the available literature. The probability of sorption of a chemical, however, can be qualitatively estimated from its sorption coefficient, K_{oc}, as derived from the equation, log K_{oc} = -0.557 log S + 4.277 (Lyman et al., 1982). If S is assumed to be 0.124×10^6 µmol/ℓ (see Section 1.2.), the K_{oc} value is ~28. Therefore, sorption is not a significant process for aquatic methyl chloride.

Pertinent data regarding the bioaccumulation of methyl chloride by aquatic organisms could not be located in the available literature as cited in the Appendix. The BCF value of 3, however, estimated from the equation, log BCF = 0.76 log K_{ow} - 0.23 (Lyman et al., 1982), with the assumption that log K_{ow} = 0.91 (see Section 1.2.) indicate that methyl chloride will not significantly bioaccumulate in aquatic organisms.

2.3. SOIL

Pertinent experimental data regarding the fate of methyl chloride in soil could not be located in the available literature as cited in the Appendix. Microorganisms isolated from soil are capable of degrading methyl chloride under aerobic and anaerobic conditions (Patel et al., 1982;

Kobayashi and Rittman, 1982). No kinetic data to evaluate the half-life for these reactions are available. Based on the fate of methyl chloride in aquatic media (see Section 2.2.), it is speculated that in soil neither photolysis, hydrolysis nor oxidation are likely to be significant. Since the number of microorganisms in soil is expected to be higher than in aquatic media, significant biodegradation of methyl chloride in soil may occur. Volatilization from soil, however, is likely to be the most important loss process. Because of its low K_{oc} and relatively high water solubility, leaching of this compound from soil to groundwater may occur from dumpsites.

2.4. SUMMARY

The sources of atmospheric methyl chloride are both natural and anthropogenic. The most important natural source of methyl chloride in the atmosphere is seawater. Combustion of both natural and manmade materials, such as burning of agricultural field residues, controlled burning of forest fires, wildfires, burning of PVC waste and building fires, contribute significantly to atmospheric methyl chloride (Lovelock, 1975; Crutzen et al., 1978; Palmer, 1976). The contribution of industrial sources to the global methyl chloride burden is very small. It has been estimated that ~0.018 million tons/year of methyl chloride is emitted globally through industrial production compared with its total emission of 5.6 million tons/year from other natural and nonindustrial sources.

Methyl chloride is reasonably stable in the atmosphere. Reaction with OH• is the most significant process for the removal of methyl chloride from the troposphere and the average tropospheric lifetime of methyl chloride that is due to this reaction is estimated to be 1.1 years. About 2% of tropospheric methyl chloride is expected to be transferred to the stratosphere where it may participate in the destruction of the ozone layer.

Of the total chlorine in the stratosphere originating from halocarbons, ~20-25% is currently contributed by methyl chloride (Crutzen and Gidel, 1983; Edwards et al., 1982).

Compared with its loss through evaporation, the loss of methyl chloride from aquatic media through photolysis, oxidation or biodegradation is insignificant. The half-life of evaporation of methyl chloride from aquatic media is ~2-3 hours (Lyman et al., 1982). Pertinent data regarding the sorption coefficient of methyl chloride in sediments or bioaccumulation factors in aquatic organisms could not be located in the available literature as cited in the Appendix. Values estimated from correlation equations (Lyman et al., 1982) predict that neither of these processes is significant in aquatic media.

In the absence of experimental data, the fate of methyl chloride in soil has been speculated from its fate in aquatic media. Evaporation from soil is likely to be the most important loss process from soil. Biodegradation in soil may be significant, but no quantitative half-life value can be estimated. Leaching of methyl chloride from soil to groundwater, although not generally likely, may occur from dumpsites.

3. EXPOSURE

3.1. AIR

From limited measurements made before 1975, NAS (1978) reported methyl chloride concentrations of 688, 1200 and 834 ppt for the continental background, marine background, and urban areas, respectively. Brodzinsky and Singh (1982) compiled the level of methyl chloride measured during and before 1980. The level of methyl chloride in urban/suburban areas and rural/remote areas of the United States was reported to be 1200 and 1100 ppt, respectively. Levels of methyl chloride concentration measured during the 1980s in the United States and other parts of the world are given in Table 3-1. The average values for the methyl chloride levels in recent years, derived from Table 3-1 and the NAS (1978) report, are as follows: 980 ppt, U.S. urban areas; 610 ppt, continental background level; and 1200 ppt, marine background. The concentration of methyl chloride in the atmosphere is dependent on seasonal, diurnal and latitudinal variations. Concentration of methyl chloride is higher in the tropics compared with higher latitudes, possibly because of higher emissions of methyl chloride from the tropical oceans (Khalil and Rasmussen, 1981). The atmospheric level of methyl chloride at a particular location is usually higher during the winter-spring period than during the summer-fall period (Lioy et al., 1983; Khalil and Rasmussen, 1981), probably because of change of local sources (such as combustion sources) of methyl chloride. Typical diurnal profiles show highest concentrations of methyl chloride during nighttime or early morning hours with minimum during the afternoon hours (Singh et al., 1982). The lower level in the afternoon hours probably reflects its decreasing concentration from its reaction with OH•.

TABLE 3-1

Recent Methyl Chloride Levels in the United States Urban Areas, in Continental Background and Other Areas of the World

Location	Date Sampled	Average Concentration (ppt)	Reference
	UNITED STATES URBAN AREAS		
Houston, TX	1980	955	Singh et al., 1982
St. Louis, MO	1980	732	Singh et al., 1982
Denver, CO	1980	763	Singh et al., 1982
Riverside, CA	1980	703	Singh et al., 1982
Staten Island, NY	1981	701	Singh et al., 1982
Pittsburgh, PA	1981	665	Singh et al., 1982
Chicago, IL	1981	856	Singh et al., 1982
Camden, NJ	1981-1982	2030	Lioy et al., 1983
Newark, NJ	1981-1982	1205	Lioy et al., 1983
Elizabeth, NJ	1981-1982	1215	Lioy et al., 1983
	Average	983	

TABLE 3-1 (cont.)

Location	Date Sampled	Average Concentration (ppt)	Reference
	CONTINENTAL BACKGROUND		
Remote Pacific Northwest, United States	1980	630	Rasmussen et al., 1981
South Pole	1980	590	Rasmassen et al., 1981
Poker Flats and Pt. Barrow, Alaska	1980	586	Khalil and Rasmussen, 1981
St. John's, Newfoundland	1980	623	Khalil and Rasmussen, 1981
Somoa	1980	642	Khalil and Rasmussen, 1981
Cape Kumakahi, Hawaii	1980	652	Khalil and Rasmussen, 1981
Cape Grim, Tasmania	1980	601	Khalil and Rasmussen, 1981
South Pole	1980	594	Khalil and Rasmussen, 1981
Pt. Barrow, Alaska	1980-1982	584	Khalil and Rasmussen, 1983
	Average	611	
	OTHER COUNTRIES		
Urban and Rural China	1980	832	Rasmussen et al., 1982
Ny Alesund, Norway	1983	731	Hov et al., 1984
The Netherlands	1980	700-3000	Guicherit and Schulting, 1985

The level of methyl chloride in the marine background is highest, suggesting that the oceans are the major source of this chemical. Localized sources may be responsible for the slightly higher values of methyl chloride in urban/surban areas or the background level.

The concentrations of methyl chloride in various indoor atmospheres have been reported by NAS (1978), and Table 3-2 shows these values. These results show that methyl chloride seems to occur in relatively higher concentrations in indoor air, because of certain local sources, with high concentrations of this compound (ppm level) found in occupational settings (OTS, 1982, 1983) where its likely to present the greatest health risks resulting from exposure (U.S. EPA, 1980b).

The daily inhalation intake of methyl chloride by an individual in the United States residing in urban/suburban areas and rural areas can be estimated on the basis of average methyl chloride concentration of 980 ppt (2.05 $\mu g/m^3$) and 610 ppt (1.27 $\mu g/m^3$), respectively, and that an individual inhales 20 m^3 per day. Based on these values, the intake of methyl chloride by the population in the United States residing in urban/suburban and rural areas will be 41 and 25 µg/day, respectively.

3.2. WATER

Based on U.S. EPA STORET data, Staples et al. (1985) used data from the 1980s only for better quality assurance and reported that of the total of 1298 industrial effluent samples, methyl chloride was detected in only 3.5% of the samples at a median concentration of <10 µg/ℓ. Similarly, of the 895 ambient water samples, only 1.4% showed detectable levels of methyl chloride at a median concentration of <10 µg/ℓ. Methyl chloride was also detected in 24/605 surface waters examined in New Jersey (Page, 1981), where the highest concentration reported was 222.4 µg/ℓ, although the

TABLE 3-2

Concentrations of Methyl Chloride in Various Indoor Atmospheres*

Sample	Concentration (ppt)
Discount Store:	
Records and automotive	>4,000
Plastic wares	>1,500
Shoes and furniture	>1,500
Restaurant:	
Tables and booth	>1,450
Movie Theater:	
Lobby before show	900
Theater before show	700
Lobby after show	1,130
Theater after show	>2,500
Air Terminal:	
Baggage and ticket area	1,240
Restaurant and waiting	1,405
Concourse	1,400
Floor Covering Store:	
Carpet storage	>1,000
Solvent shelves	1,100
Tile area	>2,000
Radio and TV Repair:	
Repair area	>4,000
Automobile Dealership:	
Display floor	>3,000
Apartment:	
During party	>2,500
After a cigarette smoked	>20,000

*Source: NAS, 1978

median concentration was below the detection limit. Methyl chloride at a maximum concentration of 12 µg/ℓ was reported in surface water in Massachusetts (Burmaster, 1982).

The concentration of methyl chloride in seawaters on the southern English coast was found to vary from 5.9×10^{-9} mℓ gas/mℓ water and 21×10^{-9} mℓ gas/mℓ water (Lovelock, 1975). Singh et al. (1979) reported the concentration of methyl chloride in the surface water of the Pacific Ocean at 26.8 mg/ℓ. Methyl chloride has also been reported in U.S. drinking water. In their National Organics Reconnaissance Survey, U.S. EPA selected these five cities: Cincinnati, OH; Miami, FL; Ottumwa, IA; Philadelphia, PA; and Seattle, WA. Methyl chloride was qualitatively detected in drinking water from all five cities (Coleman et al., 1976; U.S. EPA, 1975; Kool et al., 1982). Pellizzari et al. (1979) detected but did not quantify methyl chloride in drinking water from the New Orleans/Baton Rouge area. In Canadian drinking water, the presence of methyl chloride was reported by Otson et al. (1982). Water from 30 treatment plants was analyzed for methyl chloride, but none was detected in either raw or treated water collected during the summer. However, one of the raw water and two of the treated water collected during the winter months showed detectable levels (<5 µg/ℓ) of methyl chloride.

Methyl chloride has been reported in leachates from contaminated soils, in contaminated groundwater and in drinking water wells. Page (1981) monitored 1058 groundwaters and detected methyl chloride at a maximum concentration of 6.0 µg/ℓ in three of these waters. But the median concentration of methyl chloride in these waters was below the detection limit. Sabel and Clark (1984) qualitatively detected methyl chloride in 4/6 leachate samples, 9/13 contaminated groundwaters and 2/7 uncontaminated groundwater samples.

Methyl chloride was also reported in 1/7 leachate samples from Wisconsin at a concentration of 170 µg/ℓ (Sabel and Clark, 1984). Burmaster (1982) reported a concentration of 44 µg/ℓ in one drinking water well in Massachusetts. Greenburg et al. (1982) monitored 408 well water samples from New Jersey. Methyl chloride was qualitatively detected in a few (<10) of these well waters. It was speculated by these investigators that light chlorinated hydrocarbon including methyl chloride pollution of groundwater is likely to be found near industrial and commercial areas. Methyl chloride, in conclusion, may be present at a concentration of <5 µg/ℓ in <3% of drinking water samples, although a concentration of 44 µg/ℓ was reported in one Massachusetts drinking water well. Therefore, the majority of individuals in the United States will have no intake of methyl chloride from drinking water. Assuming a maximum concentration of 44 µg/ℓ and a daily consumption of 2 ℓ of water, a maximum possible daily exposure of 88 µg could occur in rare cases.

3.3. FOOD

Pellizzari et al. (1982) monitored mothers' milk obtained from Bridgeville, PA; Bayonne, NJ; Jersey City, NJ; and Baton Rouge, LA. Of the total of 12 samples analyzed, methyl chloride was qualitatively detected in only 2 of the samples. Other than this report, the presence of methyl chloride has not been reported in any other food samples.

3.4. SUMMARY

Methyl chloride is always present in the atmosphere at low concentrations that are dependent upon seasonal, diurnal and latitudinal variations (Khalil and Rasmussen, 1981; Lioy et al., 1983; Singh et al., 1982). The average levels of methyl chloride are 980 ppt in U.S. urban areas, 610 ppt

in continental background, and 1200 ppt in marine background. The concentrations of methyl chloride in indoor air can be higher than outdoor atmosphere (NAS, 1978). A concentration as high as 20,000 ppt has been reported inside an apartment after a cigarette was smoked (NAS, 1978). Exposure from certain occupational settings, however, is likely to present the greatest health risks resulting from exposure (U.S. EPA, 1980b). The average intake by inhalation of atmospheric methyl chloride has been estimated to be 41 µg for U.S. urban/suburban areas and 25 µg for U.S. rural areas.

Methyl chloride has been detected in a few drinking waters in the United States and Canada, though concentrations in most cases are below the detection limit, preventing quantification of the results. Methyl chloride was detected at a concentration of <5 µg/ℓ in ~3% of drinking water samples analyzed by Otson et al. (1982). Its concentration in a drinking water well in Massachusetts was reported to be 44 µg/ℓ (Burmaster, 1982). The majority of individuals in the United States will have no intake of methyl chloride from drinking water. Because methyl chloride has not been reported in any foods, it is not possible to estimate its intake from food sources.

4. PHARMACOKINETICS

4.1. ABSORPTION

Pertinent data regarding the absorption of methyl chloride by the gastrointestinal tract could not be located in the available literature as cited in the Appendix.

Methyl chloride is readily absorbed from the lungs following inhalation exposure. Putz-Anderson et al. (1981a) found that the alveolar breath levels of methyl chloride reached equilibrium within 1 hour during a 3-hour inhalation exposure of men and women. Mean±SD alveolar air levels were 63±23.6 ppm (130±48.7 mg/m³) in 24 men and women exposed to 200 ppm (413 mg/m³) and 36±12 ppm (74.3±24.8 mg/m³) in 8 individuals exposed to 100 ppm (207 mg/m³) for 3 hours. Blood levels (mean±SD) were 11.5±12.3 ppm and 7.7±6.3 ppm for the high- and low-exposure groups, respectively. In a similar experiment, the mean±SD alveolar air level of methyl chloride was 74±31.8 ppm (154±65.7 mg/m³) and the mean±SD blood level was 14.5±14.5 ppm in 12 individuals exposed to 200 ppm (413 mg/m³) for 3.5 hours. In both experiments, there was a high correlation ($r=0.85$ or 0.91, $p \leq 0.01$) between alveolar air and blood levels.

Nolan et al. (1985) also found that blood and expired air levels of methyl chloride reached equilibrium during the first hour of exposure of six male volunteers to 10 or 50 ppm (20.7 or 103 mg/m³) for 6 hours. The levels in blood and expired air were proportional to exposure. Using a 2-compartment pharmacokinetic model, Nolan et al. (1985) calculated that the individuals absorbed 1.4-3.7 µg methyl chloride/min/kg or 27.7-73.28 nmol/min/kg.

Landry et al. (1983a) exposed male Fischer 344 rats to methyl chloride vapor at 50 or 1000 ppm (103 or 2065 mg/m³) for 6 hours and measured vapor uptake at 1.5 and 2 hours of exposure. No difference in uptake rate was

detected for the two sampling times. The uptake was 200 nmol/min/kg (0.01 mg/min/kg) for the 50 ppm exposure and 3270 nmol/min/kg (0.165 mg/min/kg) for the 1000 ppm exposure. The absorption rate of methyl chloride into the blood (ppm/min/kg) is ~3 times faster in rats than in man.

Using a 2-compartment pharmacokinetic model, Landry et al. (1983a) calculated that the absorbed doses after 6 hours of exposure were 3.8 and 67 mg/kg for the 50 and 1000 ppm exposure groups, respectively. In another experiment, Landry et al. (1983a) exposed male Fischer 344 rats for 6 hours and male beagle dogs for 3 hours to methyl chloride by inhalation at 50 or 1000 ppm (103 or 2065 mg/m^3). Blood levels rose rapidly, reached a plateau and were proportional to exposure concentrations. Steady-state blood:gas concentration ratios were 1.5 and 1.8 for dogs exposed to 50 and 1000 ppm, respectively, and 1.8 and 1.9 for rats exposed to 50 and 1000 ppm, respectively. In all of the previously mentioned absorption studies, blood and expired air levels declined rapidly with the cessation of exposure.

4.2. DISTRIBUTION

Continued exposure to methyl chloride results in a rapid uptake by the blood, though only moderate blood levels are detected (U.S. EPA, 1980a). Distribution of methyl chloride to organs is extensive. Levels of methyl chloride (expressed as mmol/100 g) in the organs of dogs after several hours (exact time not specified) of inhalation exposure to 15,000 ppm (30,975 mg/m^3) were 0.089 in the liver, 0.081 in the heart, 0.093 in the brain and 0.13 in the blood (von Oettingen et al., 1950). Sperling et al. (1950) injected dogs intravenously with the pure gas at dose levels ranging from 1650-2730 mg (~183.3 mg/kg) or as a mixture in propylene glycol (as a vehicle) at doses of 59-110 mg (~14.7 mg/kg). The disposition of methyl chloride followed the same pattern whether given as pure gas or in a vehicle, disappearing from the bloodstream with extreme rapidity with 90%

lost almost immediately and 98% in about an hour. Methyl chloride was detected in the brain, heart, liver, spleen, stomach and blood immediately after injection (Sperling et al., 1950). Levels were generally $\leq$0.02 mg/g tissue immediately after exposure and at 60 minutes after exposure.

Bus (1978) exposed male Fischer 344 rats to ^{14}C-methyl chloride vapor for 6 hours at a concentration of 1500 ppm (3098 mg/m^3). At 24 hours after exposure, the levels of radioactivity (dpm/g wet weight) were 5606 in liver, 4253 in kidney, 2436 in lung, 2131 in heart and 1363 in brain. The level in the blood was 1346 dpm/mℓ.

Kornbrust et al. (1982) stated that unpublished observations from their laboratory indicated that considerable amounts of the recovered radioactivity were still detected in the carcasses and major organs of rats 2 days after inhalation exposure to ^{14}C-methyl chloride. This observation prompted them to investigate whether the persistence of radioactivity was due to direct binding of ^{14}C-methyl chloride to long-lived macromolecules or to incorporation of the radioactive carbon atom into macromolecules by normal anabolic processes. Male Fischer 344 rats were exposed by inhalation to ^{14}C-methyl chloride at 500 ppm (1033 mg/m^3) for 6 hours. The rats were killed immediately after exposure. Total uptake of radioactivity (as µmol ^{14}C-methyl chloride equivalents/g wet weight) in whole tissue homogenates following exposure was 1.21 for lung, 4.13 for liver, 3.43 for kidney, 2.29 for testes, 0.71 for muscle, 0.57 for brain and 2.42 for intestine. The radioactivity was associated with lipid, RNA, DNA and protein. Pretreatment of the rats with inhibitors of protein, lipid and nucleic acid synthesis inhibited the uptake of radioactivity into the various macromolecules, indicating that the uptake arose from metabolism of methyl chloride through the one-carbon pool.

Bus et al. (1982) demonstrated the transplacental transfer of methyl chloride in Fischer 344 rats. The rats were exposed to 0 or 1500 ppm (3098) for 6 hours on gestation day 19. The dams were killed at 2, 4 and 8 hours after exposure, and maternal and fetal tissue were analyzed for NPSH levels, which are known to be depleted by methyl chloride (Section 4.3.). Maternal liver and kidney and fetal placental NPSH levels were maximally decreased immediately, while fetal liver and carcass levels were maximally decreased at 2 hours after exposure.

4.3. METABOLISM

Methyl chloride metabolism has been widely investigated in vivo and in vitro. Redford-Ellis and Gowenlock (1971a) indicated that the reaction of ^{14}C-methyl chloride with rat tissue homogenates resulted in the formation of ^{14}C-S-methylglutathione and ^{14}C-S-methylcysteine as the primary products in the liver, kidney and brain tissues. Thus, methyl chloride reacted with NPSH, primarily glutathione. When incubation mixtures were heated, formation of S-methylglutathione and S-methylcysteine was inhibited, indicating that the reactions were enzyme catalyzed. Kidney and brain homogenates, but not liver homogenates, hydrolyzed S-methylglutathione to S-methylcysteine. This observation indicates that S-methylcysteine is formed directly in the liver, but that S-methylcysteine in the brain and kidney may arise from hydrolysis of S-methyl glutathione. Landry et al. (1983a) reported that rats exposed to 0, 50, 225, 600 or 1000 ppm (0, 103, 465, 1239 or 2065 mg/m^3) ^{14}C-methyl chloride for 6 hours were evaluated for tissue NPSH, total tissue radioactivity and urinary metabolites. Methyl chloride depleted NPSH in liver, kidney, testis and epididymis in a dose-related manner. Metabolites in urine were identified as N-acetyl-S-methyl-cysteine, methylthioacetic acid sulfoxide and N-(methylthioacetyl)glycine, which were formed by the reaction between methyl chloride and glutathione.

Redford-Ellis and Gowenlock (1971b) also demonstrated that methyl chloride reacted with NPSH in human plasma and erythrocytes to form S-methylglutathione and S-methylcysteine. Van Doorn et al. (1980) detected S-methylcysteine in the urine of workers occupationally exposed to methyl chloride.

Dodd et al. (1982) exposed Fischer 344 rats to 100, 500 or 1500 ppm (207, 1033 or 3098 mg/m³) of methyl chloride for 6 hours. The treatment lowered liver, kidney and lung NPSH *in vivo* in a concentration-related manner, while blood NPSH was not affected by treatment, indicating a tissue-specific reaction between methyl chloride and sulfhydryl groups. When rats were pretreated with Arochor-1254 or SKF-525A, modifiers of microsomal enzymes, the decrease in NPSH levels was not altered, which suggests that formation of a reactive intermediate by cytochrome P-450 was not required for glutathione conjugation, as was suggested by U.S. EPA (1980b).

Kornbrust and Bus (1982) investigated the possibility that formic acid is a metabolite of methyl chloride in male Fischer 344 rats exposed by inhalation up to 10,000 ppm (20,650 mg/m³) for 3 hours. No significant increase in the blood or urine formic acid levels were observed in exposed rats compared with controls. When folate-dependent metabolism of formic acid was inhibited by pretreatment with nitrous oxide or antifolate methotrexate, however, concentrations of formic acid in blood and urine of methyl chloride-exposed rats were increased. Inhibition of formic acid metabolism also inhibited the incorporation of ^{14}C into the tissue macromolecules of rats exposed by inhalation to ^{14}C-methyl chloride. Pretreatment with nitrous oxide combined with intraperitoneal injection of sodium formate (to dilute the ^{14}C-formic acid derived from ^{14}C-methyl chloride) resulted in reduced expiration of $^{14}CO_2$ and increased excretion of urinary radioactivity. These results indicate a pathway in rats in which methyl chloride

is metabolized to formic acid, which in turn is metabolized by folic acid-dependent processes, leading to incorporation of the carbon atom into macromolecules or oxidation to CO_2.

Evtushenko (1967) found elevated levels of formaldehyde in the blood of rats exposed by inhalation to methyl chloride. As suggested by Kornbrust and Bus (1983), methyl chloride may be metabolized by subsequent metabolism of methylglutathione to formaldehyde, which may be converted to formic acid. Kornbrust and Bus (1983) found that methyl chloride was metabolized to formaldehyde at a linear rate for 60 minutes in the presence of rat liver microsomes. The production of formaldehyde was NADPH-dependent, was increased in microsomes prepared from rats pretreated with 3-methylcholanthrene or phenobarbital (inducers of microsomal enzymes) and was inhibited by SKF-525A, carbon monoxide, hexabarbital and metyrapone (inhibitors of cytochrome P-450). Thus, the formation of formaldehyde was dependent on cytochrome P-450. The formation of formaldehyde was also highly dependent on the availability of glutathione. Based upon these results, results of previously described studies that indicate conjugation with glutathione and cysteine, and current knowledge of S-methylcysteine metabolism, Kornbrust and Bus (1983) proposed the pathway depicted in Figure 4-1.

4.4. EXCRETION

Very little unchanged methyl chloride is excreted by any route. Sperling et al. (1950) (see Section 4.2.) reported that very little unchanged methyl chloride was excreted in the expired air, urine or bile of dogs following intravenous injection.

Landry et al. (1983b) studied the pharmacokinetics of methyl chloride in rats exposed for 6 hours and dogs exposed for 3 hours to 50 or 1000 ppm (103 or 2065 mg/m^3). As indicated in Section 4.1., blood levels of methyl

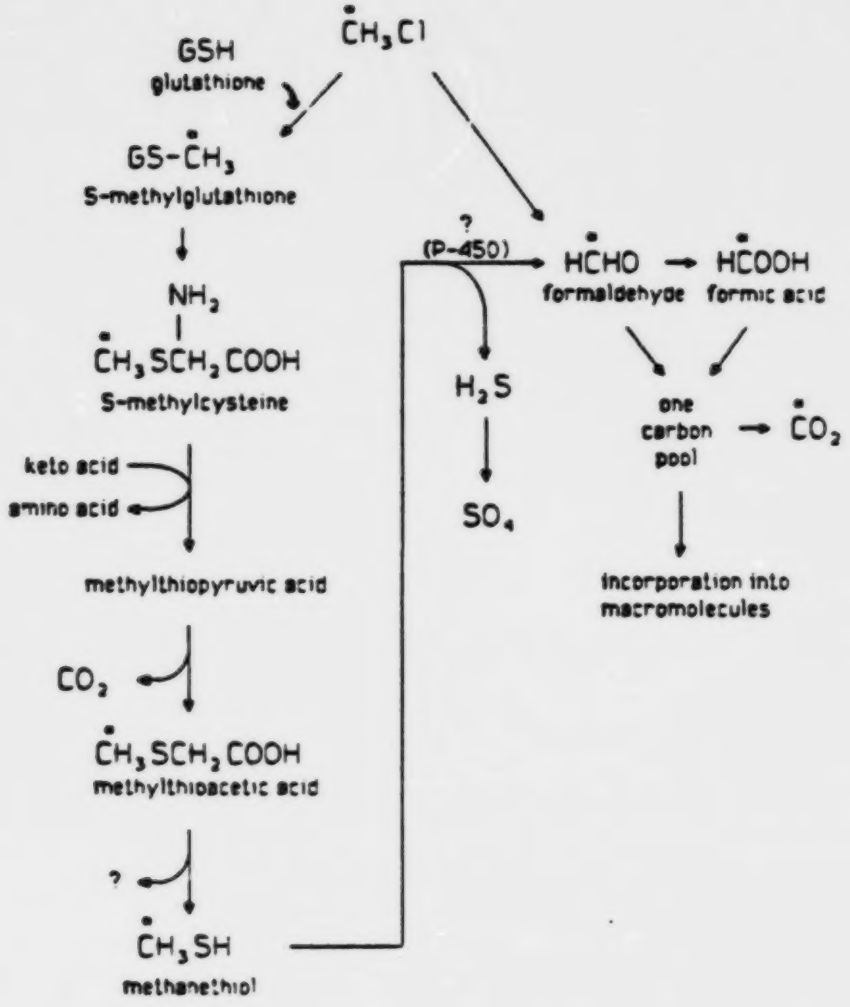


FIGURE 4-1

Proposed Scheme for the Metabolism of Methyl Chloride

Source: Kornbrust and Bus, 1983

*Indicates the position of the radioactive label

chloride rose rapidly and reached steady-state concentrations proportionate to exposure levels. The plateau was reached within minutes and was maintained throughout the exposure. When exposure ceased, the blood concentrations declined rapidly in a biphasic, nonconcentration dependent manner. The disappearance of methyl chloride from blood followed a linear 2-compartment open model. Half-lives for the α- and β-elimination phases were 4 and 15 minutes, respectively, in rats and 8 and 40 minutes, respectively, in dogs.

Similar results were obtained in human volunteers exposed to 10 or 50 ppm (20.7 or 103 mg/m^3) for 6 hours (Nolan et al., 1985) with rapid, biphasic elimination of methyl chloride from the blood and in the expired air. The half-life for the β-phase of the blood elimination was 50-90 minutes.

As discussed by Landry et al. (1983b), the pharmacokinetics of unchanged methyl chloride are different from that of radioactivity derived from ^{14}C-methyl chloride. According to Bus (n.d.), blood levels of radioactivity did not reach equilibrium in rats exposed to 1500 ppm (3098 mg/m^3) ^{14}C-methyl chloride for 6 hours. Following exposure, however, radioactivity levels in the blood remained constant for 4 hours and then declined in a biphasic manner. The half-life for the β-phase was 17.6 hours. To explain the lag in the elimination of radioactivity, it was suggested that the extensive metabolism of ^{14}C-methyl chloride (see Section 4.3.) lead to temporary accumulation of radioactive metabolites in the tissues.

Excretion of radioactivity by rats was rapid following exposure to ^{14}C-methyl chloride at 1500 ppm (3098 mg/m^3) for 6 hours (Bus, 1978). At 24 hours after exposure, very little radioactivity remained in the tissues. Pulmonary excretion of radioactivity amounted to 63.9% of the total excretion and was essentially complete at 18 hours after exposure.

Urinary excretion of radioactivity amounted to 32% of the total excreted; of this amount, 61% was recovered in the first 8 hours after exposure. Fecal excretion amounted to 3.9% of the total radioactivity excreted.

4.5. SUMMARY

Pertinent data regarding the absorption of methyl chloride from the gastrointestinal tract could not be located in the available literature as cited in the Appendix. Following inhalation exposure of rats, dogs and humans, methyl chloride was rapidly absorbed from the lungs with steady-state blood and expired air levels reached within 1 hour during exposure (Putz-Anderson et al., 1981a,b; Nolan et al., 1985; Landry et al., 1983a). The blood and expired air levels remained at steady-state until exposure was terminated and then declined rapidly in a biphasic manner. Using 2-compartment pharmacokinetic models, Nolan et al. (1985) calculated that humans exposed to 10 or 50 ppm (20.7 or 103 mg/m^3) absorbed 1.4-3.7 μg methyl chloride/min/kg (27.7-73.28 nmol/min/kg) while Landry et al. (1983a) calculated uptakes 200 nmol/min/kg (0.01 mg/min/kg) and 3270 nmol/min/kg (0.165 ng/min/kg) in rats exposed to 50 and 1000 ppm (103 and 2065 mg/m^3), respectively.

Following absorption, methyl chloride is rapidly and extensively distributed to organs and tissues (U.S. EPA, 1980b). At 2 days following inhalation exposure of rats to ^{14}C-methyl chloride, radioactivity was still detected in tissues and the carcasses of rats; the persistence of radioactivity was due to incorporation of the radioactive carbon atom into macromolecules by normal anabolic processes rather than to direct binding of ^{14}C-methyl chloride to the macromolecules (Kornbrust et al., 1982). Bus et al. (1982) demonstrated the transplacental transfer of methyl chloride in rats.

Methyl chloride is extensively metabolized. Metabolism appears to involve reaction of methyl chloride with glutathione and cysteine to yield S-methylglutathione and S-methylcysteine and other sulfur-containing metabolites (Redford-Ellis and Gowenlock, 1971a,b; Landry et al., 1983a; Dodd et al., 1982) which can be excreted in the urine (Landry et al., 1983a; Van Doorn et al., 1980). Subsequent metabolism of S-methylcysteine may lead to cytochrome P-450 dependent metabolism of methanethiol to formaldehyde and formic acid, whose carbon atoms enter the one-carbon pool for incorporation into macromolecules or formation of CO_2 (Kornbrust and Bus, 1983). Methyl chloride may also be metabolized directly to formaldehyde, which in turn is oxidized to formic acid.

Very little unchanged methyl chloride is excreted in expired air, urine or bile (Sperling et al., 1980). Blood and expired air levels of methyl chloride declined rapidly when inhalation exposure of rats, dogs or humans ceased (Landry et al., 1983b; Nolan et al., 1985). The elimination was biphasic; half-lives for the β-phase were 15 minutes in rats, 40 minutes in dogs and 50-90 minutes in humans. The pharmacokinetics of radioactivity derived from ^{14}C-methyl chloride are markedly different (Landry et al., 1983b; Bus, n.d.). Blood levels of radioactivity in rats did not reach steady state during inhalation exposure, but remained constant for 4 hours following exposure and then declined in a biphasic manner with a β-phase half-life of 17.6 hours (Bus, n.d.). Extensive metabolism of ^{14}C-methyl chloride may have led to a temporary accumulation of metabolites in tissues, accounting for the lag in elimination. Excretion of radioactivity following 6 hours inhalation exposure of rats was essentially complete in 18 hours; 63.9, 32 and 3.9% of the total excreted radioactivity were excreted in the expired air, urine and feces, respectively (Bus, 1978).

5. EFFECTS

5.1. CARCINOGENICITY

Pertinent data regarding the potential carcinogenicity of methyl chloride by oral exposure could not be located in the available literature as cited in the Appendix.

A 2-year inhalation toxicity and oncogenicity study in rats and mice, which was conducted for CIIT at the Battelle Memorial Institute Columbus Laboratories. The chronic study was initiated in July 1978 and interim reports were published by Pavkov et al. (1980, 1981). The final report including histological and pathological data was published by CIIT (1983).

In this study, groups of 120 female and 120 male B6C3F1 mice and 120 female and 120 male Fisher 344 rats were exposed to methyl chloride vapor at concentrations of 0, 50, 225 or 1000 ppm (0, 103, 465 or 2065 mg/m^3, respectively) for 6 hours/day, 5 days/week. Interim kills of ~5-20 animals/sex/group were performed at 6, 12, 18 and 24 months. Body weight, clinical signs of toxic effects and mortality were followed throughout the study for both rats and mice. Comprehensive histological examination was made of all control and 1000 ppm mice and rats that died or were sacrificed during the study. For the 50 and 225 ppm groups, histological examination was limited to selected target organs (testes, epididymis, kidneys, liver and lungs for rats and liver, kidneys, spleen and brain for mice). Hematological, clinical chemistry and urine analyses were done on animals randomly preselected for necropsy at 6, 12, 18 and 24 months of exposure.

Treated male mice had significantly increased incidences of renal tumors compared with controls, while no increased incidences of tumors were observed in female mice or male or female rats. Survival was significantly reduced only in the 1000 ppm female mice. Survival of the 1000 ppm male

mice was also reduced, but the difference from control survival was not significant because control male mice also had high early mortality, which was attributed to fighting. Because of the high mortality most of the mice in the 1000 ppm group were terminated at 21 months. The numbers of male mice sacrificed or dying in each month from the 12th month (when the first kidney tumor was observed) onward are presented in Table 5-1; the prevalence of kidney tumors is included. The tumors were categorized as renal cortex adenomas, renal cortex adenocarcinomas, papillary cystadenomas, tubular cystadenomas and papillary cystadenocarcinomas. The overall incidence of kidney tumors (adenoma or carcinoma), excluding the mice that died or were killed before the 12th month are 0/67 in the control group, 0/61 in the 50 ppm group, 2/57 in the 225 ppm group and 18/82 in the 1000 ppm group (see Table 5-1). These incidences, however, do not account for kidney tumors that may have developed had the mice that were sacrificed at interim kills or that died during the experiment lived to 24 months. In order to correct for the intercurrent mortality, the method described by Peto et al (1980) was used and resulted in the incidences presented in Table 5-2.

NIOSH (1984) presented an extensive review of the final report by CIIT (1983) and the U.S. EPA Office of Toxic Substances has done considerable work in reviewing the health effects of methyl chloride including this 2-year CIIT study. In their review documents, U.S. EPA concluded that this cancer bioassay study was valid for health assessment purposes under TSCA (U.S. EPA, 1980b, 1984b).

5.2. MUTAGENICITY

Mutagenicity studies of methyl chloride are summarized in Table 5-3. Methyl chloride was positive for reverse mutation in Salmonella typhimurium strains TA1535 (Andrews et al., 1976) and TA100 (Simmon et al., 1977;

TABLE 5-1

Numbers of Male Mice Sacrificed or Dying and Kidney Tumor Prevalence in Each Month from the 12th Month Onward[a,b]

Month	Treatment Group			
	Control	50 ppm	225 ppm	1000 ppm
13	12	10	10	11 (1A)
14	1	0	0	3
15	3	0	0	4
16	0	0	0	2
17	2	0	0	3 (1A,1C)
18	1	0	0	3
19	6	5	5	11 (3A)
20	3	4	2	17 (4A)
21	6	5	1	24 (4A,4C)
22	3	0	3	3
23	4	1	0	0
24	26	36	36 (2A)	1
Total	67	61	57	82

[a]Source: NIOSH, 1984

[b]Parentheses indicate numbers of mice with kidney tumors, classified as adenomas (A) or carcinomas (C).

TABLE 5-2

Incidence of Benign or Malignant Kidney Tumors in Male B6C3F1 Mice Exposed by Inhalation to Methyl Chloride (99.99% Pure) for up to 24 Months[a,b]

Exposure (ppm, 6 hours/day, 5 days/week)	Tumor Incidence[c]
0	0/67
50	0/67
225	2/57
1000	22/82 ($p=4.5\times10^{-7}$)

QUALITY OF EVIDENCE

Strength of Study: The compound was tested in both sexes of two species by a relevant route at several exposure levels for a significant portion of the lifespan. The number of animals was large. Histopathological examination was comprehensive in control and 1000 ppm groups, and was performed on target organ in the 50 and 225 ppm group.

Weakness of Study: Early mortality in high-dose group

Overall Adequacy: Adequate

[a]Source: NIOSH (1984)

[b]The duration of exposure was the same as the length of the experiment

[c]Mice that died before the 12-month interim kill were excluded. Tumor incidences were adjusted for intercurrent mortality by the method of Peto et al. (1980).

[d]Statistically different from control by Fischers Exact Test performed at SRC.

TABLE 5-3

Mutagenicity Testing of Methyl Chloride

Assay	Indicator/Organism	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Reverse mutation	Salmonella typhimurium TA100	vapor phase in dessicators	0-20%	± S-9	+ +	The response was slightly higher in the presence of S-9	Simmon, 1978, 1981; Simmon et al., 1977
Reverse mutation	S. typhimurium TA1535	vapor phase	0.5-20.7%	± S-9	+ +	The response was higher in the presence of S-9	Andrews et al., 1976
Forward mutation	S. typhimurium TM677	vapor phase	0-20%	none	+	NC	Fostel et al., 1985
Forward mutation	TK6 human lymphoblastoid cells	vapor phase	1-5%	none	+	NC	Fostel et al., 1985
SCE	TK6 human lymphoblastoid cells	vapor phase	0.3-3%	none	+	NC	Fostel et al., 1985
DNA strand breaks	TK6 human lymphoblastoid cells	vapor phase	1-5%	none	-	Detected by alkaline elution method	Fostel et al., 1985
Dominant lethal	F-344 rat	treatment of males by inhalation	0, 1000 or 3000 ppm (0, 2065 or 6195 mg/m³), 6 hours/day for 5 days	NA	+	Pattern of pre- and postimplantation losses and known cytotoxic effects of methyl chloride indicatethat losses are due in part to cytotoxic effect	Working et al., 1985a,b

NC = No comment; NA = not applicable

Simmon, 1978,1981) in the presence and absence of S-9. Fostel et al. (1985) reported that methyl chloride was positive for forward mutations in S. typhimurium TA677 and human lymphoblasts and for SCE in human lymphoblasts without metabolic activation. No increase occurred in DNA strand breaks in the human cells when analyzed by alkaline elution.

Methyl chloride was reported by Working et al. (1985a,b) as an inducer of dominant lethal mutations in mature sperm of F-344 rats (40 males/group) exposed to 3000 ppm (6195 mg/m³) for 6 hours/day for 5 days.

5.3. TERATOGENICITY

Inhalation teratogenicity tests in mice and rats indicate that methyl chloride is not teratogenic in rats, but is teratogenic in mice at concentrations not associated with maternal toxicity. Wolkowski-Tyl et al. (1983a) exposed groups of 25 Fischer 344 female rats and groups of 33 C57BL/6 female mice to 0, 100, 500 or 1500 ppm (0, 207, 1033 or 3098 mg/m³) methyl chloride for 6 hours/day on days 7-19 of gestation (rats) or 6-17 (mice). Rats were sacrificed on day 20 and mice were sacrificed on day 18 of gestation. Maternal and fetal toxicity occurred at the highest exposure level in rats and included reduced food consumption and body weight gain of dams, reduced fetal body weights and crown-rump length of fetuses ($p<0.05$). No treatment-related external, skeletal or visceral abnormalities were observed in the fetuses, but evidence of delayed development (reduced ossification in limbs and thoracic vertebrae and sternebrae) was observed in the 1500 ppm fetuses; the incidences were significantly greater than controls ($p<0.05$).

In mice, all dams exposed to 1500 ppm were killed in extremis on gestation days 10-14 and had histological evidence of neural damage. No evidence of maternal, embryo or fetal toxicity was observed in the 100 or 500 ppm

groups, but a significantly (statistically) increased incidence of heart defects in litters of the 500 ppm group was reported. The authors concluded that methyl chloride at 500 ppm, but not at 100 ppm, was teratogenic in mice, resulting in malformation of the heart.

In a second study, female C57BL/6 mice (74-77/group) that had been mated to C3H male mice were exposed 6 hours/day to levels of 0, 250, 500 or 750 ppm (0, 516, 1033 or 1549 mg/m^3) of methyl chloride on days 6-18 of gestation (Wolkowski-Tyl et al., 1983b). Dams exposed to 750 ppm had decreased body weights, hypersensitivity to touch or sound, tremors, convulsions and ataxia; seven died or were killed _in extremis_ during the exposure period. All other dams were sacrificed on day 18 of gestation. There was a significant exposure-related ($p<0.05$) increase in the number and percentage of affected (nonlive plus malformed) fetuses per litter at 750 ppm. The 750 and 500 ppm groups had statistically significant ($p<0.05$) increased incidences of heart defects compared with the control group. No differences in pregnancy rate, gravid uterine weight, implantation rate, resorption rate, dead fetuses, nonlive (dead plus reabsorbed), live fetuses, sex-ratio or average fetal body weight were observed in any group. Therefore, methyl chloride was teratogenic to mice at inhalation exposures of 500 and 750 ppm, 6 hours/day and toxic to dams at 750 ppm. No maternal, embryo or fetal toxicity or teratogenicity was associated with exposure of mice to 250 ppm of methyl chloride.

5.4. REPRODUCTIVE EFFECTS

Several short-term inhalation studies of methyl chloride have been performed to study the effects on reproduction in the male rat. Morgan et al. (1982) exposed groups of 10 male Fischer rats by inhalation to methyl chloride at 0, 2000, 3500 or 5000 ppm (0, 4130, 7228 or 10,325 mg/m^3), 6 hours/day for 5 days, to filtered air for 2 days, and to methyl chloride

again for 4 days. The rats were killed after the last exposure. Upon histological examination, 20/20 rats at 2000 and 3500 ppm had minimal testicular degeneration, while 10/10 rats at 5000 ppm had severe testicular degeneration. No lesions were found in controls. Chapin et al. (1984) exposed adult male F-344 rats to 3500 ppm (7228 mg/m³) methyl chloride 6 hours/day for 5 days, to filtered air for 3 days, and to methyl chloride again for 6 hours/day for 4 days. Controls were exposed to filtered air. Groups of 6-8 treated rats and 2 control rats were sacrificed on days 5, 7, 9, 11, 13, 15, 19 and 70 after exposure. Histopathological examination of the testis revealed a delay in spermiation and varying degrees of disruption and disorganization of the seminiferous epithelium which were evident in all treated rats by day 9-13. Rats killed on day 19 had granulomas of the epididymis, while rats killed at 70 days had shrunken seminiferous tubules (70-90%), varying degrees of recovery of spermatogenesis (10-30%) and evidence of chronic granulomata in the epididymus. Serum levels of testosterone decreased in a time-related manner during five consecutive exposures to methyl chloride. Testicular and epididymal tissue in controls appeared normal.

Reproductive effects of inhaled methyl chloride in male Fischer 344 rats were investigated by Working et al. (1985a). Groups of 40 male rats were exposed to methyl chloride at 0, 1000 or 3000 ppm (0, 2065 or 6195 mg/m³), 6 hours/day for 5 days. Each male was bred to a single untreated female every week for 8 weeks and the standard criteria of dominant lethal tests were recorded. Exposure to 1000 ppm methyl chloride caused no consistent change in any parameter relative to control values. Exposure to 3000 ppm methyl chloride caused a slight increase in postimplantation loss at week 1 postexposure (sperm exposed in the epididymis or vas deferens) and increases in preimplantation loss throughout the 8 weeks. Fertility of the 3000 ppm

methyl chloride-exposed males was significantly decreased by week 2 post-exposure and never recovered to control values during the observation period. The authors (Working et al., 1985) noted that although inhalation exposure to 3000 ppm methyl chloride induced dominant lethal mutations in sperm exposed in the vas deferens and epididymis, it did not do so in sperm exposed within the testis. The authors concluded that this atypical pattern of pre- and postimplantation losses in the high-dose group, and an inflammation of the epididymis that caused sperm granuloma, suggests a nongenetic (cytotoxic) mechanisms may also be contributing to the preimplantation fetal loss.

In a second study, Working et al. (1985b) exposed groups of 40 male rats to methyl chloride vapor at 0, 1000 or 3000 ppm, 6 hours/day for 5 days to study sperm quality and testicular histopathology. Five rats from each group were killed every week for 8 weeks and five each from the control and 3000 ppm group were also examined at week 16 postexposure. Males exposed to 1000 ppm exhibited no consistent difference from controls in the functional morphology of the testes or the spermatozoa, while exposure to 3000 ppm caused over 50% incidence of uni- or bilateral granulomas in the cauda epididymis by the 8th week. Significantly depressed testes weights were observed by 3 weeks postexposure and declined steadily until 8 weeks post-exposure; however, testes weights had recovered to near control values by week 16 after exposure. Delayed spermiation was followed by increasing severity of disruption and disorganization of the seminiferous epithelium. By week 7, 60-70% of the spermatogonial stem cells were destroyed. There were significantly decreased numbers of sperm and increased incidences of abnormal sperm in the vas deferens by week 1. Sperm motility was depressed and the incidence of headless tails was increased at week 3. Recovery to various degrees was observed in these parameters at later sacrifices, with a

return to nearly normal by week 16; however, sperm counts remained depressed. The authors concluded that high concentrations of inhaled methyl chloride produced considerable and lasting cytotoxicity in rat testes and epididymal epithelium; however, almost all measures of sperm quality and testicular histopathology returned to normal by 16 weeks after exposure.

Hamm et al. (1985) conducted a modified 2-generation reproduction study in Fischer 344 rats. Groups of 40 males and 80 females were exposed by inhalation to methyl chloride concentrations of 0, 150, 475 or 1500 ppm (0, 310, 981 or 3098 mg/m^3), 6 hours/day, 5 days/week for 10 weeks and then 7 days/week. At 10 weeks, each male was mated to two exposed females for 2 weeks, after which 10 males/group were killed and necropsied. Exposure was discontinued for the remaining 30 males/group, which were then mated with unexposed females for 2 weeks. After an additional nonexposure period of 10 weeks, 10 males/group were necropsied and 20 males/group were mated with unexposed females. The procedure was repeated after another 18 weeks of no exposure. The exposure for the treated females was continued from the start of mating until gestation day 18 and from postnatal day 4-28. F_1 pups were not exposed directly by inhalation before weaning. After weaning, however, 40 male and 80 female F_1 rats were exposed to 150 ppm and 23 male and 46 female F_1 rats were exposed to 475 ppm (no litters were born to 1500 ppm F_0 rats) for 10 weeks, following the same protocol as used for the F_0 generation. Females without copulatory plugs were not included in analysis of fertility.

Body weight gain was significantly depressed in 1500 ppm F_0 males and females after 2 weeks and in 475 ppm males and females after 57 days. Exposed and unexposed F_0 females mated to 1500 ppm males produced no litters, while exposed and unexposed F_0 females mated to 475 ppm males

produced significantly fewer litters than controls. The 1500 ppm F_0 males were sterile, while the 475 ppm males had lower fertility than controls. There was no effect on fertility in the 150 ppm exposed males; however, there was a lower than normal fertility rate in the F_0 controls. This result may be significant in that the poor fertility rates in the F_0 controls may have biased the detection of an effect in the 150 ppm exposed males. There was no effect on litter size, sex ratio, pup viability, pup survival or pup growth in the 150 and 475 ppm groups. F_0 males exposed to 1500 ppm had atrophy of seminiferous tubules (10/10), granulomas in the epididymis (3/10), decreased testes weight, and greatly reduced sperm numbers. For the recovery breedings, the 1500 ppm F_0 males had partially recovered fertility. Histopathological lesions of the necropsied males were similar to those observed after the first necropsy. Findings for the F_1 generation breedings were statistically or biologically insignificant.

5.5. CHRONIC AND SUBCHRONIC TOXICITY

Pertinent data regarding the oral toxicity of methyl chloride could not be located in the available literature as cited in the Appendix. Because methyl chloride exists as a gas and is used in the industrial setting, primary concern has been focused on its toxicity by inhalation.

In an epidemiology experiment, Repko et al. (1976) studied the behavioral and neurogical effects of methyl chloride in human subjects occupationally exposed to methyl chloride for 1 month to >25 years. Data from a total of 171 workers (122 exposed, 49 controls) from several locations (age ranged from 18-61 years) were compiled for analysis. Measured ambient concentrations of methyl chloride ranged from 1.8-70 ppm (3.7-145 mg/m³) with an average of 33.57 ppm (69.3 mg/m³). The mean breath concentration of methyl chloride was 13.32 ppm (28.3 mg/m³). The results indicated that

duration of employment was correlated significantly with airborn methyl chloride ($p<0.005$) and methyl chloride in the breath ($p<0.01$). Breath levels were significantly correlated with airborn levels ($p<0.005$). There were no significant differences found for the neurological examinations or EEG activity. Results of behavioral tests indicated that exposed workers had impaired performances on time-sharing tasks and increased magnitudes of finger tremors compared with controls. Ambient levels of methyl chloride in air were correlated with poor performance.

In a chronic study, groups of 120 male and 120 female Fischer 344 rats and 120 male and 120 female B6C3F1 mice were exposed to vapors of methyl chloride 6 hours/day, 5 days/week for up to 24 months (Pavkov et al., 1980, 1981; CIIT, 1983; NIOSH, 1984). The exposure levels were 0, 50, 225 or 1000 ppm (0, 103, 465, 2065 mg/m^3) for both rats and mice. Interim kills were performed after 6, 12, 18 and 24 months of exposure (see Section 5.1. for details). Controls were exposed to clean air and were subjected to the same procedure as the tested groups of rats and mice. The animals were observed or evaluated for clinical signs, body weight gain and mortality throughout the study, for ophthalmalogical, hematological clinical chemistry and urinalysis parameters before each kill, for gross and histopathological lesions at each sacrifice (see Section 5.1.) and for neurofunction at 18 and 24 months. Mortality rate was not affected by exposure in rats, whereas both male and female mice had increased mortality at the 1000 ppm exposure level. For rats and mice of both sexes exposed to 1000 ppm, a consistent trend for reduced body weight gain was observed. Consistent trends for reduced body weight gain were not observed for other groups. Neurofunctional impairment was observed at 18, 21 and 22 months among almost all male and female mice exposed to 1000 ppm; the impairment consisted of weakened extensor thrust/scratch response and a positive clutch response at 18 months.

No exposure-related effect was observed in mice exposed to the lower levels or in male and female rats at all exposure levels. Significantly elevated SGPT levels occurred at 6, 12 and 18 months in male mice exposed to 1000 ppm; these increases were correlated with liver lesions. In female mice, at all levels of exposure SGPT was significantly increased at 6 and 12 months, but not at 18 or 24 months; furthermore, no correlation with microscopic lesion was apparent. No other treatment-related changes in clinical chemistry, hematology or urinalysis parameters were observed in mice or rats. Relative organ weight changes that were considered to be treatment-related were as follows: increased heart weight in 1000 ppm female mice at 18 months and 225 ppm female mice at 24 months; decreased testes weights in 1000 ppm male rats at 24 months; increased liver weight in 1000 ppm female mice at 18 months; decreased liver weight in 50 ppm male rats at 24 months; decreased kidney weights in 1000 ppm male mice at 6 months and in 1000 ppm female rats at 24 months; increased kidney weight in 1000 ppm female mice at 18 months and increased lung weight in 50 and 225 ppm male rats at 6 months. Results of the ophthalmological examinations revealed no clear-cut treatment-related abnormalities in either species.

There were significantly increased overall incidences of hepatic lesions consisting of multifocal centrilobular hepatocellular necrosis, karyomegaly, cytomegaly and vacuolar degeneration in male and female 1000 ppm mice compared with controls ($p<0.0001$). In the kidney, 1000 ppm male mice had significantly increased incidences of hyperplasia and karyomegaly of renal tubule epithelial cells compared with controls ($p<0.0001$). These lesions were first observed at 12 months and the severity increased with longer exposure. High-dose male mice also had significantly increased incidences of degeneration and atrophy of seminiferous tubules ($p=0.001$) and of the spleen ($p<0.0001$) compared with controls. Increased incidences of degenera-

tion of the cerebellar granular layer occurred in high-dose males ($p<0.0001$) and females ($p<0.05$) compared with controls. The only treatment-related histopathological lesion in rats was a significantly increased incidence of atrophy and degeneration of the seminiferous tubules of male rats at 1000 ppm.

Results of a study in which several different species were exposed by inhalation to methyl chloride 6 hours/day, 6 days/week for up to 64 weeks were presented in a series of reports by Smith and von Oettingen (1947a,b), Smith (1947) and Dunn and Smith (1947). The exposure levels were 4000 ppm (8260 mg/m^3) (19 rats and 6 rabbits), 3000 ppm (6195 mg/m^3) (20 guinea pigs, 20 mice, 6 dogs, 10 rats and 4 rabbits), 2000 ppm (4130 mg/m^3) (81 guinea pigs, 109 mice, 9 dogs, 5 monkeys, 59 rats, 12 rabbits, 4 cats), 1000 ppm (2064 mg/m^3) (46 guinea pigs, 32 mice, 12 dogs, 4 rabbits and 18 rats), 500 ppm (1033 mg/m^3) (22 guinea pigs, 34 mice, 6 dogs, 2 monkeys, 5 rabbits and 18 rats) and 300 ppm (620 mg/m^3) (guinea pigs, mice, dogs, monkey, rabbits and rats; numbers not reported). Mortality data were reported by Smith and von Oettingen (1947a). At $\geq$1000 ppm, deaths occurred in all species as early as 1-37 days. At 500 ppm, deaths occurred in most species tested beginning at 6-211 days; no rats exposed to 500 ppm died. Younger animals tended to be more resistant than adults. Generally, guinea pigs, mice, dogs and monkeys were more susceptible than rats and rabbits. At 300 ppm, no effects were apparent in guinea pigs, mice, dogs, monkeys, rabbits or rats after 64 weeks of exposure. Smith and von Oettingen (1947b) described the overt signs of toxicity displayed by the animals exposed to $\geq$500 ppm. Dogs exposed to 500 ppm for up to 29 weeks had marked neuromuscular effects, including ataxia, severely impaired gait, tremors and spasticity. Monkeys exposed to 500 ppm became emaciated and prostrated before death at 16-17 weeks, but no spasticity or convulsions were observed.

Neuromuscular dysfunction was also observed in guinea pigs, mice, dogs, rabbits and rats exposed to ≥1000 ppm. No signs of toxicity were observed in any of the species exposed to 300 ppm for 64 weeks. Smith (1947) failed to find any treatment-related effects on hematological or clinical chemistry parameters in any of the species. Dunn and Smith (1947) reported the results of the histological examinations. No histopathological lesions were observed in the brains of monkey or dogs that had neuromuscular dysfunction. Rats exposed to 500 or 1000 ppm and guinea pigs exposed to 500 ppm for up to 9 months did not have histopathological lesions in unspecified tissues. Rats and mice exposed to 2000 ppm for up to 9 months had necrosis of renal tubules and fatty metamorphosis of the liver. The animals exposed to 300 ppm were not examined for histopathological lesions.

Evtushenko (1966) exposed groups of 10 rats and groups of 4 rabbits to 240 or 40 mg/m³ methyl chloride 4 hours/day for up to 6 months. In rats, exposure to either concentration resulted in decreased erythrocyte count and depletion of lymphoid elements in spleen and lymph. In both species at 240 mg/m³, there was disturbed excretory function of the liver. Rabbits had discoloration of the optic disc and histological lesions of the retina and optic nerve at both exposure levels.

Mitchell et al. (1979) exposed groups of 10 male and 10 female Fischer 344 rats (6 weeks of age) and 10 male and 10 female B6C3F1 mice (6 weeks of age) for 6 hours/day, 5 days/week for 13 weeks to methyl chloride vapor at 375 ppm (774 mg/m³), 750 ppm (1549 mg/m³) or 1500 ppm (3098 mg/m³). Equal numbers of controls were subjected to clean air. Rats and mice were observed for food consumption, body weight gain, clinical signs and mortality. At 13 weeks, blood and urine samples were taken for hematological and clinical chemistry analysis, ophthalmic examinations were made and the

animals were killed for organ weight determinations and gross and histological examination. Examinations were comprehensive for control and high-dose animals; target organs and tissues determined from examination of the high-dose animals were examined in the low- and middle-dose groups. Treatment-related effects of the high-dose group were significantly increased SGPT activity in male mice, increased relative liver weights of male and female mice and female rats, hepatic infarctions in one male mouse and one female rat, and increased incidence and severity of cytoplasmic vacuolization of hepotocytes in male mice. No dose-response relationship in hematological, clinical chemistry or urinalysis parameters were clearly observed in the middle- or low-dose groups. Rats of both sexes in the 750 and 1500 ppm groups had significantly reduced body weight gain compared with controls. No other treatment-related effects were observed.

5.6. OTHER RELEVANT INFORMATION

Landry et al. (1985) evaluated the relationship between methyl chloride exposure duration and neurotoxicity. A group of 12 female C57BL/6 mice were exposed to methyl chloride for 11 days, either continuously (22 hours/day) to levels of 0-200 ppm (0-413 mg/m^3), or intermittently (5.5 hours/day) to different levels ranging from 0-2400 ppm (0-4956 mg/m^3). Histopathological examination revealed granular cell layer degeneration in mice exposed continuously to 100 ppm (207 mg/m^3) or intermittently to 400 ppm (826 mg/m^3), while no effect was observed in mice exposed continuously to 50 ppm (103 mg/m^3) or intermittently to 150 ppm (310 mg/m^3). The treatment decreased average body and thymus weights in mice exposed continuously to 150 ppm or intermittently to 2400 ppm. At 2400 ppm, exposed mice developed hemeglobinuria resulting from intravascular hemolysis, but not hematuria (because there were no intact red cells in the urine samples).

Repko (1981) and Repko and Lasley (1979) reviewed several human case history intoxication reports of methyl chloride under a variety of exposure conditions ranging from 1-810 minutes. The effects of methyl chloride on the CNS, among other body organs, are well documented in these reviews.

Putz-Anderson (1981b) investigated the behavioral effects of inhaling either 100 or 200 ppm (207 or 413 mg/m³) methyl chloride on volunteers (average age 22 years) for 3 hours. The results indicate that the 200 ppm concentration had a marginally significant effect on performance (measured as visual vigilance, dual task, and discrimination) compared with controls.

5.7. SUMMARY

Inhalation exposure of mice to methyl chloride at 0, 50, 225 or 1000 ppm (0, 103, 465 or 2065 mg/m³), 6 hours/day, 5 days/week for 2 years resulted in a statistically significant increased incidence of benign and malignant kidney tumors in the high-dose male mice compared with controls (Pavkov et al., 1981; CIIT, 1981; NIOSH, 1984). No carcinogenic effect was observed in female mice or male and female rats similarly treated. Methyl chloride was positive for reverse mutations in Salmonella typhimurium strains TA100 and TA1535 with and without metabolic activation (Andrews et al., 1976; Simmon et al., 1977), for forward mutation in S. typhimurium TM677 and human lymphoblasts, for SCE in human lymphoblasts without activation (Fostel et al., 1985) and for dominant lethal mutations in male rats (Working et al., 1985a,b). Methyl chloride was teratogenic to the offspring of mice exposed by inhalation to 500 or 750 ppm (1033 or 1549 mg/m³), 6 hours/day during gestation, resulting in increased incidences of dead and malformed fetuses and heart defects (Wolkowski-Tyl et al., 1983a,b). Exposure levels $\geq$750 ppm were toxic to dams. No effects were observed at $\leq$250 ppm, 6 hours/day. No teratogenic effects were observed in the offspring of rats exposed to 100,

500 or 1500 ppm (207, 1033 or 3098 mg/m³) 6 hours/day during gestation; however, maternal toxicity (reduced body weight gain) and fetotoxicity (reduced fetal body weight, reduced crown-rump length and delayed ossification) were observed at 1500 ppm (Wolkowski-Tyl et al., 1983b). Short-term inhalation exposure (5-9 days) of male rats to ≥2000 ppm (4130 mg/m³), 6 hours/day resulted in testicular degeneration, epididymal granuloma, abnormal sperm and reduced fertility (Morgan et al., 1982; Chapin et al., 1984; Working et al., 1985a,b). No effects on reproductive function or testicular morphology were observed at 1000 ppm, 6 hours/day (Working et al., 1985b). In a 2-generation study, male rats exposed to 1500 ppm (3098 mg/m³), 6 hours/day for 5-7 days/week for 10-12 weeks, and mated to exposed or unexposed females were infertile, while males exposed to 475 ppm (981 mg/m³) had reduced fertility (Hamm et al., 1985). The infertility was found to be partially reversible. Treatment-related histopathological lesions in the testis and epididymis were found only in 1500 ppm F_0 males. No adverse effects were observed in the F_1 generation.

In a 2-year inhalation study, male and female rats and mice were exposed to methyl chloride at 0, 50, 225 or 1000 ppm (0, 103, 465 or 2065 mg/m³), 6 hours/day, 5 days/week for up to 2 years (Pavkov et al., 1980, 1981; CIIT, 1983; NIOSH, 1984). Effects in male rats that were considered to be treatment-related were significantly decreased relative liver weight at 50 ppm at 24 months, increased relative kidney weights at 50 and 225 ppm at the 6-month kill, decreased relative testes weight at 1000 ppm at 24 months, decreased body weight gain and atrophy and degeneration of the seminiferous tubules. The only effects in female rats were decreased body weight gain and decreased relative kidney weight at 24 months in the 1000 ppm group. In mice, no effects were observed at 50 ppm, while the only effect at 225 ppm

was an increased relative heart weight of females at 24 months. At 1000 ppm, males and females had increased mortality and neurofunctional impairment. Males had increased levels of SGPT and males and females had liver lesions consisting of centrilobular necrosis, karyomegaly, cytomegaly and vacuolar degeneration. Other treatment-related lesions at 1000 ppm included hyperplasia and karyomegaly of the renal epithelium and degeneration of seminiferous tubules in males and degeneration of the cerebellar granular layer in males and females.

Inhalation exposure to $\geq$500 ppm ($\geq$1032 mg/m^3), 6 hours/day, 6 days/week, were fatal to rabbits, guinea pigs, mice, dogs, monkeys and cats, with the first deaths occurring in 1-211 days (Smith and von Oettingen, 1947a,b). No rats died at 500 ppm, while all species tested survived 300 ppm (620 mg/m^3), 6 hours/day, 6 days/week for 64 weeks. Exposures $\geq$500 ppm were associated with severe neuromuscular impairment. In a 13-week study, rats exposed to $\geq$750 ppm (1549 mg/m^3), 6 hours/day, 5 days/week, had decreased body weight gain (Mitchell et al., 1979). Rats and mice exposed to 1500 ppm (3098 mg/m^3) had increased liver weights and increased incidences of vacuolization of hepatocytes.

Occupational exposure to an average airborne concentration of 33.57 ppm (69.3 mg/m^3) has been associated with impaired performance of time-sharing tasks and increased magnitudes of finger tremors (Repko et al., 1976).

6. AQUATIC TOXICITY

6.1. ACUTE

Little information about the toxicity of methyl chloride to aquatic organisms could be located in the available literature. Dawson et al. (1977) reported a 96-hour LC_{50} of 550 mg/ℓ for bluegills, Lepomis macrochirus, in a static test. The same authors reported a 96-hour LC_{50} of 270 mg/ℓ for the tidewater silverside, Menidia beryllina. A concentration of 450 mg/ℓ caused 100% mortality in this species in 1 hour. Bringmann and Kuehn (1980) found that the concentration of methyl chloride that inhibited cell multiplication in the protozoan Entosiphon sulcatum was >8000 mg/ℓ.

6.2. CHRONIC

Pertinent data regarding the chronic toxicity of methyl chloride to aquatic organisms could not be located in the available literature as cited in the Appendix.

6.3. PLANTS

Bringmann and Kuehn (1976, 1980) reported toxicity thresholds for inhibition of cell multiplication in various species. These concentrations were 550 mg/ℓ for the blue-green alga Microcystis aeruginosa (Bringmann and Kuehn, 1976), 1450 mg/ℓ for the green alga Scenedesmas quadricauda and 500 mg/ℓ for the bacterium Pseudomonas putida (Bringmann and Kuehn, 1980).

6.4. RESIDUES

Pertinent data regarding methyl chloride residue in aquatic biota could not be located in the available literature as cited in the Appendix.

6.5. SUMMARY

Very little information concerning toxicity of methyl chloride to aquatic organisms could be located in the available literature. LC_{50} values of 550 mg/ℓ and 270 mg/ℓ were reported for bluegills and tidewater silverside, respectively (Dawson et al. 1977). Toxicity thresholds for algae and bacteria are in the range of 500-1450 mg/ℓ (Bringmann and Kuehn, 1976, 1980).

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

The Occupational Safety and Health Administration (OSHA, 1985) does not list a permissible exposure limit for methyl chloride.

ACGIH (1985) has adopted 50 ppm (105 mg/m³) as the 8-hour TWA-TLV and 100 ppm (205 mg/m³) for 15 minutes as the STEL.

The TLV was recommended by ACGIH (1980) based on the body of human exposure data that indicate no irreversible systemic effects at 100-200 ppm, along with the observations of Repko et al. (1976) that neurotoxic effects may occur at lower exposures.

An ADI for methyl chloride of 0.54 mg/kg/day or 37.8 mg/day for 70-kg reference man was derived by U.S. EPA (1982) from the ACGIH (1980) TLV of 50 ppm (105 mg/m³) associated with equivocal evidence for performance impairment in humans. An uncertainty factor of 10 was applied. The inhaled dose was estimated by assuming that workers inhale 10 m³ during the workday, work 5 days/week and absorb 50% of the inhaled chemical. The U.S. EPA (1985) has retained this ADI (0.54 mg/kg/day) at the present time.

7.2. AQUATIC

Pertinent data regarding standards and criteria for the protection of aquatic biota from the effects of methyl chloride could not be located in the available literature as cited in the Appendix.

8. RISK ASSESSMENT

Pertinent data regarding the potential carcinogenicity of methyl chloride by oral exposure could not be located in the available literature as cited in the Appendix. Methyl chloride has been clearly shown to be carcinogenic in male mice exposed by inhalation. Inhalation exposure of mice to methyl chloride at 0, 50, 225 or 1000 ppm (0, 103, 465 or 2065 mg/m³), 6 hours/day, 5 days/week for 2 years resulted in a statistically significant increased incidence of benign and malignant kidney tumors in the high-dose male mice compared with controls (see Section 5.1.) (U.S. EPA, 1980b, 1984b; Pavkov et al., 1981; CIIT, 1983; NIOSH, 1984). No carcinogenic effect was observed in female mice or male and female rats similarly treated. Methyl chloride was positive for reverse mutations in Salmonella typhimurium strains TA100 and TA1535 with and without metabolic activation (Andrews et al., 1976; Simmon et al., 1977), for forward mutation in S. typhimurium TM677 and human lymphoblasts, for SCE in human lymphoblasts without activation (Fostel et al., 1985) and for dominant lethal mutations in male rats (Working et al., 1985a,b). Methyl chloride was teratogenic to the offspring of mice exposed by inhalation to 500 or 750 ppm (1033 or 1549 mg/m³), 6 hours/day during gestation, resulting in increased incidences of dead and malformed fetuses and heart defects (Wolkowski-Tyl et al., 1983a,b). Exposure levels $\geq$750 ppm were toxic to dams. No effects were observed at $\leq$250 ppm 6 hours/day. No teratogenic effects were observed in the offspring of rats exposed to 100, 500 or 1500 ppm (207, 1033 or 3098 mg/m³) 6 hours/day during gestation; however, maternal toxicity (reduced body weight gain) and fetotoxicity (reduced fetal body weight, reduced crown-rump length and delayed ossification) were observed at 1500 ppm

(Wolkowski-Tyl et al., 1983b). Short-term inhalation exposure (5-9 days) of male rats to ≥2000 ppm (4130 mg/m³), 6 hours/day resulted in testicular degeneration, epididymal granuloma, abnormal sperm and reduced fertility (Morgan et al., 1982; Chapin et al., 1984; Working et al., 1985a,b). No effects on reproductive function or testicular morphology were observed at 1000 ppm, 6 hours/day (Working et al., 1985b). In a 2-generation study, male rats exposed to 1500 ppm (3098 mg/m³), 6 hours/day for 5-7 days/week for 10-12 weeks and mated to exposed or unexposed females were infertile, while males exposed to 475 ppm (981 mg/m³) had reduced fertility (Hamm et al., 1985). The infertility was found to be partially reversible. Treatment-related histopathological lesions in the testis and epididymis were found only in 1500 ppm F_0 males. No adverse effects were observed in the F_1 generation.

In a 2-year inhalation study, male and female rats and mice were exposed to methyl chloride at 0, 50, 225 or 1000 ppm (0, 103, 465 or 2065 mg/m³), 6 hours/day, 5 days/week for up to 2 years (Pavkov et al., 1980, 1981; U.S. EPA, 1980b, 1984b; CIIT, 1983; NIOSH, 1984). Effects in male rats that were considered to be treatment-related were significantly decreased relative liver weights at 50 ppm at 24 months, increased relative kidney weights at 50 and 225 ppm at the 6-month kill, decreased relative testes weights at 1000 ppm at 24 months, decreased body weight gain and atrophy and degeneration of the seminiferous tubules. The only effects in female rats were decreased body weight gain and decreased relative kidney weights at 24 months in the 1000 ppm group. In mice, no effects were observed at 50 ppm, while the only effect at 225 ppm was increased relative heart weights of females at 24 months. At 1000 ppm, males and females had increased mortality and neurofunctional impairment. Males had increased levels of SGPT and

males and females had liver lesions consisting of centrilobular necrosis, karyomegaly, cytomegaly and vacuolar degeneration. Other treatment-related lesions at 1000 ppm included hyperplasia and karyomegaly of the renal epithelium and degeneration of seminiferous tubules in males and degeneration of the cerebellar granular layer in males and females.

Inhalation exposures to $\geq$500 ppm ($\geq$1032 mg/m^3), 6 hours/day, 6 days/week were fatal to rabbits, guinea pigs, mice, dogs, monkeys and cats, with the first deaths occurring between 1 and 211 days (Smith and von Oettingen, 1947a,b). No rats died at 500 ppm, while all species tested survived 300 ppm (620 mg/m^3) 6 hours/day, 6 days/week for 64 weeks. Exposures $\geq$500 ppm were associated with severe neuromuscular impairment. In a 13-week study, rats exposed to $\geq$750 ppm (1549 mg/m^3), 6 hours/day, 5 days/week had decreased body weight gain (Mitchell et al., 1979). Rats and mice exposed to 1500 ppm (3098 mg/m^3) had increased liver weights and increased incidences of vacuolization of hepatocytes.

Occupational exposure to an average airborne concentration of 33.57 ppm (69.3 mg/m^3) has been associated with impaired performance of time-sharing tasks and increased magnitudes of finger tremors (Repko et al., 1976).

Because methyl chloride has been demonstrated to be carcinogenic to male mice (Pavkov et al., 1981; CIIT, 1983; U.S. EPA, 1980b, 1984a; NIOSH, 1984), it is appropriate to derive a q_1^* to estimate the increased lifetime risk of cancer for human exposure to methyl chloride. The data used to derive the q_1^* are presented in Table 8-1. As discussed in Section 5.1., the data in Table 8-1 reflect the incidences of kidney tumors corrected for intercurrent mortality by the method of Peto et al. (1980).

The transformed doses in Table 8-1 were calculated by expanding the exposure over a 24-hour day and a 7-day week, by multiplying by the inhalation rate (0.039 m^3/day) of a 0.03 kg mouse (U.S. EPA, 1980c) and by an

TABLE B-1

Cancer Data Sheet for Derivation of q_1^*

Compound: methyl chloride

Reference: CIIT, 1983

Species, Strain, Sex: mouse, B6C3F1, male

Body weight: 0.03 kg (measured)

Length of exposure (le) = 24 months

Length of experiment (Le) = 24 months

Lifespan of animal (L) = 24 months

Tumor site and type: kidney, adenoma or carcinoma

Route, vehicle: inhalation, air

Experimental Doses or Exposures (mg/m^3, 6 hours/day, 5 days/week)	Transformed Dose (mg/kg/day)	Incidence No. Responding/No. Examined
0	0	0/67
103	12	0/61
656	76	2/57
2065	240	22/82

Unadjusted q_1^* from study = 9.5356155×10^{-4} $(mg/kg/day)^{-1}$

Human q_1^* = 1.2647587×10^{-2} $(mg/kg/day)^{-1}$

absorption factor of 0.5 and by dividing by the mouse body weight of 0.03 kg as estimated from the growth curve in the report by Pavkov et al. (1980). The unadjusted q_1^* was calculated using the multistage model developed by Howe and Crump (1982). The q_1^* value for humans of 1.26×10^{-2} $(mg/kg/day)^{-1}$ was calculated by multiplying the unadjusted q_1^* data by the cube root of the ratio of the reference human body weight (70 kg) to the mouse body weight (0.03 kg). In an alternate approach, NIOSH (1984) recommended that the tumor incidences only for the mice that died or were killed between 12 and 21 months be used to obtain a more similar age-distribution of the treated groups if the multistage stage model is used to estimate risk. This approach resulted in the tumor incidences presented in Table 8-2. Using these data in the multistage model resulted in an unadjusted q_1^* of 8.91×10^{-4} $(mg/kg/day)^{-1}$. The human q_1^* of 1.76×10^{-2} $(mg/kg/day)^{-1}$ was calculated by multiplying the unadjusted value by the cube root of body weight ratio and by $(L/Le)^3$. The correction of lifespan was made in this case because the duration of exposure was less than the lifespan. Without the correction for lifespan, the human q_1^* is 1.81×10^{-2} $(mg/kg/day)^{-1}$.

The approach used by NIOSH (1984), however, results in tumor incidences that exclude from the denominator the majority of the mice in the control, low and middle groups. Furthermore, the approach excludes the two middle dose mice in which kidney tumors were observed at the final sacrifice. Therefore, the more realistic human q_1^* of 1.26×10^{-2} $(mg/kg/day)^{-1}$, generated from the data corrected for intercurrent mortality (see Table 8-1) is recommended for estimating the increased lifetime risk of human exposure to methyl chloride.

TABLE 8-2

Cancer Data Sheet for Derivation of q_1^*

Compound: methyl chloride

Reference: NIOSH, 1984; CIIT, 1983

Species, Strain, Sex: mouse, B6C3F1, male,

Body weight: 0.03 kg (measured)

Length of exposure (le) = 21 months

Length of experiment (Le) = 21 months

Lifespan of animal (L) = 24 months

Tumor site and type: kidney, adenoma or carcinoma

Route, vehicle: inhalation, air

Experimental Doses or Exposures (mg/m^3, 6 hours/day, 5 days/week)	Transformed Dose (mg/kg/day)	Incidence No. Responding/No. Examined
0	0	0/34
103	12	0/24
656	76	0/18
2065	240	18/78

Unadjusted q_1^* from study = 8.9109087×10^{-4} $(mg/kg/day)^{-1}$

Human q_1^* = 1.7642363×10^{-2} $(mg/kg/day)^{-1}$

9. REPORTABLE QUANTITIES

9.1 REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

Studies of oral exposure to methyl chloride could not be located in the available literature; however, chronic, subchronic, teratogenicity and reproduction studies of inhalation exposure to methyl chloride and a study of human occupational exposure were available. These studies were discussed in Chapter 5 and are summarized in Table 9-1.

The transformed animal doses were calculated from the inhalation exposures by expanding the concentrations in mg/m³ over a 24-hour day and a 7-day week, by multiplying by the inhalation rate of the animal and by dividing by the animal body weight. The inhalation rates of mice and rats were calculated according to the formulae recommended by U.S. EPA (1980c). The inhalation rates for all other animal species were based on data compiled by Durkin (1985). The transformed dose for the human exposure concentration was calculated by multiplying by 10 m³/day (the assumed breathing rate in an 8-hour workday) and by 5 days/7 days, and by dividing by 70 kg. The equivalent human doses (see Table 9-1) were calculated by multiplying the transformed animal dose by the cube root of the ratio of the animal body weight to the reference human body weight.

The study in rats and rabbits by Evtushenko (1966) is unsuitable for consideration in the RQ determination because the reliability of the results is uncertain; similar effects were not observed in rats treated chronically at much higher concentrations.

The data used to calculate the RQ are presented in Table 9-2. The MEDs were calculated by multiplying the equivalent human dose by 70 kg to express the MED in mg/day.

TABLE 9-1

Inhalation Toxicity Summary for Methyl Chloride

Species/ Strain	Sex	No. at Start	Average Weight (kg)	Purity	Exposure	Transformed Animal Dose (mg/kg/day)	Equivalent Human Dose (mg/kg/day)	Response	Reference
Rat/F344	M	120/ group	0.30[a]	99.97%	50, 225 or 1000 ppm (103, 465 or 2065 mg/m³) 6 hours/day, 5 days/week for up to 24 months	12	1.9	Increased relative liver weight at 24 months, increased relative kidney weight at 6 months	Pavkov et al., 1980, 1981; CIII, 1983
						56	9.1	Increased relative kidney weight at 6 months	
						247	40	Decreased relative testes weight at 24 months, decreased body weight gain; atrophy and degeneration of seminiferous tubules	
Rat/F344	F	120/ group	0.22[a]	99.97%	50, 225 or 1000 ppm (103, 465 or 2065 mg/m³) 6 hours/day, 5 days/week for up to 24 months	14	2.1	No effect	Pavkov et al., 1980, 1981; CIII, 1983
						62	9.1	No effect	
						275	40.3	Decreased body weight gain; decreased relative kidney weight at 24 months	
Rat/NR	NR	18	0.35[b]	NR	1000 ppm (2065 mg/m³) 6 hours/day, 6 days/ week for >175 days	282	48.2	33% died within 24-175 days; reduced growth rate	Smith and von Oettingen, 1947a,b; Smith, 1947; Dunn and Smith, 1947
Rat/F344	M	10/ group	0.22[a] 0.19[a]	≥99%	750 or 1500 ppm (1549 or 3098 mg/m³) 6 hours/day, 5 days/ week for 13 weeks	206 or 431	30.2 60.1	Decreased body weight gain in both groups	Mitchell et al., 1979
Rat/F344	F	10/ group	0.15[a] 0.14[a]	≥99%	750 or 1500 ppm (1549 or 3098 mg/m³) 6 hours/day, 5 days/ week for 13 weeks	234 478	30.2 60.2	Decreased body weight gain Increased relative liver weight, decreased body weight gain; hepatic infarction in one rat	Mitchell et al., 1979
Rat/NR	NR	10/ group	0.35[b]	NR	40 or 240 mg/m³, 4 hours/day for 6 months	4.2 or 25.5	0.7 4.4	Decreased erythrocyte count, depletion of lymphoid elements in spleen and lymph at both doses; disturbed excretory function of liver at 25.5 mg/kg/day	Evtushenko, 1966

0732p 06/04/86

TABLE 9-1 (cont.)

Species/ Strain	Sex	No. at Start	Average Weight (kg)	Purity	Exposure	Transformed Animal Dose (mg/kg/day)	Equivalent Human Dose (mg/kg/day)	Response	Reference
Rat/F344	F	25/ group	0.17[a]	>99.99%	1500 ppm (3098 mg/m³) 6 hours/day, on gestation days 7-20	629	84.5	Reduced food consumption and body weight gain of dams; reduced fetal body weights and crown-rump length of fetuses	Wolkowski-Tyl et al., 1983b
Rat/F344	M	40/ group	0.22[a] 0.185[a]	99.98%	475 or 1500 ppm (981 or 3098 mg/m³) 6 hours/day, 5 days/week for 10 weeks then 7 days/week for 2 weeks	139 466	20.4 64.4	Depressed body weight gain; reduced fertility, no histopathological lesions in testes Depressed body weight gain; 100% sterlity, partially reversible, atrophy of seminiferous tubules, epidydimal granulomas, reduced testes weight	Hamm et al., 1985
Rat/F344	F	80/ group	0.13[a] 0.118[a]	99.98%	475 or 1500 ppm (981 or 3098 mg/m³) 6 hours/day, 5 days/week for 10 weeks then 7 days/week for ~4.5 weeks	197 622	24.2 64.4	Reduced body weight gain at both doses	Hamm et al., 1985
Mouse/ B6C3F1	M+F	120/ sex/ group	0.03[a]	99.97%	50, 225 or 1000 ppm (103, 465 or 2055 mg/m³) 6 hours/day, 5 days/week for up to 24 months	24 108 479	1.8 8.1 36.1	No effects Increased relative heart weight of females at 24 months Increased mortality; neurofunctional impairment, increased SGPT levels, liver lesions (centrilobular necrosis, karyomegaly, vacuolar degeneration, degeneration of seminiferous tubules, degeneration of cerebellar granullar layer, kidney lesions	Pavkov et al., 1980, 1981; CIIT, 1983
Mouse/NR	NR	34	0.03[b]	NR	500 ppm (1033 mg/m³) 6 hours/day, 6 days/week for >266 days	288	21.7	High mortality; neuromuscular impairment	Smith and von Oettingen, 1947a,b; Smith, 1947; Dunn and Smith, 1947
Mouse/ B6C3F1	M+F	10/ sex/ group	0.02[a]	≥99%	1500 ppm (3098 mg/m³) 6 hours/day, 5 days/week for 13 weeks	830	54.7	Increased SGPT levels, increased relative liver weight, increased incidence and severity of hepatocyte vacuolization; one mouse had an hepatic infarction	Mitchell et al., 1979

0732p
06/04/86

TABLE 9-1 (cont.)

Species/ Strain	Sex	No. at Start	Average Weight (kg)	Purity	Exposure	Transformed Animal Dose (mg/kg/day)	Equivalent Human Dose (mg/kg/day)	Response	Reference
Mouse/ C57Bl/6	F	33-77/ group	0.02[a]	≥99.99%	500 or 750 ppm (1033 or 1549 mg/m³) 6 hours/day during gestation	387	25.4	Increased number of dead and malformed fetuses; increased incidence of heart defects; no maternal toxicity	Wolkowski-Tyl, 1983a,b
						581	38.2	Increased number of dead and malformed fetuses; increased incidence of heart defects; severe maternal toxicity	
Guinea pig/NR	NR	22	0.84[b]	NR	500 ppm (1033 mg/m³) 6 hours/day, 6 days/week for ≥266 days	105	24	Reduced survival	Smith and von Oettingen, 1947a,b; Smith, 1947; Dunn and Smith, 1947
Rabbit/ NR	NR	4	3.8[b]	NR	500 ppm (1033 mg/m³) 6 hours/day, 6 days/week for ≥266 days	116	44	Reduced survival, neuromuscular impairment	Smith and von Oettingen, 1947a,b; Smith, 1947; Dunn and Smith, 1947
Rabbit/ NR	NR	NR	3.8[b]	NR	40 or 240 mg/m³, 4 hours/day for 6 months	3.5	1.3	Histological lesions in retina and optic nerve	Evtushenk, 1966
						21	8.0	Histological lesions in retina and optic nerves, disturbed excretory function of liver	
Dog/NR	NR	4	12.7[b]	NR	500 ppm (1033 mg/m³) 6 hours/day, 6 days/week ≥203 days	75	42.5	Reduced survival, severe neuromuscular impairment	Smith and von Oettingen, 1947a,b; Smith, 1947; Dunn and Smith, 1947
Monkey/ NR	NR	2	8.0[b]	NR	500 ppm (1033 mg/m³) 6 hours/day, 6 days/week for 210 days	149	72.3	50% mortality by day 110, emaciation, prostration	Smith and von Oettingen, 1947a,b; Smith, 1947; Dunn and Smith, 1947
Human	M+F	122	70[b]	NR	33.57 ppm (69.3 mg/m³) during 8-hour work shift	7.1	7.1	Impaired performance on time-sharing tasks and increased magnitude of finger tremor	Repko et al., 1976

[a]Estimated from data provided by the investigators

[b]Reference values for rats, mice and humans from U.S. EPA (1980c) and for all other species from Durkin (1985)

0732p 04/03/86

TABLE 9-2

Inhalation Composite Scores for Methyl Chloride

Species	Animal Dose (mg/kg/day)	Equivalent Human Dose (mg/kg/day)	Chronic Human MED (mg/day)	RV_d	Effect	RV_e	CS	RQ	Reference
Mouse	288	21.7	1520	1	Increased mortality	10	10	1000	Smith and von Oettingen, 1947a,b
Rat	139	20.4	143*	2.3	Reduced fertility	8	18.4	1000	Hamm et al., 1985
Rat	466	64.4	451*	1.5	100% sterility	9	13.5	1000	Hamm et al., 1985
Rat	12	1.9	133	2.3	Increased relative liver weight	4	9.2	1000	Pavkov et al., 1980, 1981

*The dose was divided by an uncertainty factor of 10.

The most severe effect of methyl chloride exposure is increased mortality, which warrants an RV_e of 10. The lowest equivalent human dose for increased mortality is 21.7 mg/kg/day, obtained from the data for mice in the study by Smith and von Oettingen (1947a,b). Although the exposure was less than chronic, it is not necessary to divide the MED of 1520 mg/day by an uncertainty factor because effects of chronic exposure of mice to higher and lower doses as determined by Pavkov et al. (1980, 1981) are known. The MED corresponds to an RV_d of 1. Multiplying the RV_d by the RV_e results in a CS of 10, which corresponds to an RQ of 1000.

The next most severe effect that occurred at a lower equivalent dose is decreased fertility/rats, which warrants an RV_e of 8. This effect occurred at an equivalent human dose of 20.4 mg/kg/day in the study of Hamm et al. (1985). It is necessary to divide this dose by an uncertainty factor of 10 because fertility was not evaluated in the chronic study of Pavkov et al. (1980, 1981). The resultant MED is 143 mg/day, which corresponds to an RV_d of 2.3. Multiplying the RV_d by the RV_e results in a CS of 18.4, which corresponds to an RQ of 1000.

Rats treated at a higher dose in the Hamm et al. (1985) study were completely sterile and had histopathological lesions in the testis and epididymis. The RV_e is 9. Multiplying the equivalent human dose of 64.4 mg/kg/day by 70 kg and dividing by an uncertainty factor of 10 results in a MED of 451 mg/day, which corresponds to an RV_d of 1.5. The CS is 13.5 and the RQ is 1000.

An increase in organ weights, which warrants an RV_e of 4, is the only less severe effect observed at lower equivalent human doses. The lowest dose is 1.9 mg/kg/day in the study by Pavkov et al. (1980, 1981). Multiplying by 70 kg results in an MED of 133, which corresponds to an RV_d of 2.3. The CS is 9.2, which corresponds to an RQ of 1000.

As seen from Table 9-2, the highest CS was obtained using the data for reduced fertility of rats in the study by Hamm et al. (1985), which is recommended as the basis of the RQ for methyl chloride (Table 9-3).

In a previous derivation of the RQ (U.S. EPA, 1983), the study by Smith and von Oettingen (1947a,b) was used as the basis of the RQ. The current determination had a broader and more recent database for consideration.

9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY

The carcinogenicity of methyl chloride to mice was demonstrated in a chronic inhalation study (Pavkov, 1980, 1981; CIIT, 1981; NIOSH, 1984). In this study, treated male mice had increased incidences of kidney tumors while no increased incidences of tumors were observed in female mice or in male or female rats. Groups of 120 male and 120 female B6C3F1 mice and 120 male and 120 female Fischer 344 rats were exposed to methyl chloride vapor at concentrations of 0, 50, 225 or 1000 ppm (0, 103, 465 or 2065 mg/m^3), 6 hours/day, 5 days/week for up to 24 months. Interim kills of 5-20 animals/sex/group were performed at 6, 12, 18 and 24 months. In addition, most of the 1000 ppm male and female mice were terminated at 21 months because of high mortality. Comprehensive histopathological examination of control and 1000 ppm rats and mice and histopathological examination of target organs (including the kidney) of the 50 and 225 ppm groups were performed on all animals that died or were sacrificed during the study. Survival was significantly reduced only in the 1000 ppm female mice. Survival of the 1000 ppm male mice was also reduced, but the difference from control survival was not significant because control male mice also had high mortality, which was attributed to fighting. The numbers of male mice sacrificed or dying in each month from the 12th month (when the first kidney tumor was observed)

TABLE 9-3

Methyl Chloride

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	inhalation
Dose*:	143 mg/day
Effect:	reduced fertility
Reference:	Hamm et al., 1985
RV_d:	2.3
RV_e:	8
Composite Score:	18.4
RQ:	1000

*Equivalent human dose

onward are presented in Table 5-1; the prevalence of kidney tumors is included. The tumors were categorized as renal cortex adenomas, renal cortex adenocarcinomas, papillary cystadenomas, tubular cystadenomas and papillary cystadenocarcinomas.

The overall incidence of kidney tumors (adenoma or carcinoma), excluding the mice that died or were killed before 12 months are 0/67 in the control group, 0/61 in the 50 ppm group, 2/57 in the 225 ppm group and 18/22 in the 1000 ppm group (see Table 5-1). These incidences, however, do not account for kidney tumors that may have developed had the mice that were sacrificed at interim kills or that died during the study lived to 24 months. In order to correct for the intercurrent mortality, the method described by Peto et al. (1980) was used and resulted in the incidences presented in Table 5-2. Although methyl chloride was not carcinogenic to female mice or rats, the incidence and site of tumors in male mice indicate that the data are sufficient to classify methyl chloride as a Group C possible human carcinogen based on the data provided in the CIIT (1983) study and the NIOSH (1984) review and according to the U.S. EPA (1984a) Proposed Guidelines for Carcinogen Risk Assessment. The qualitative assessment of a "possible human carcinogen" (Group C) is further supported by a number of positive genotoxic studies and an SAR (structure-activity relationship) to methyl bromide, which is a suspected human carcinogen (Holder, 1984).

The data are adequate to derive a potency factor for methyl chloride (Table 9-4). The transformed doses were calculated by multiplying the exposure concentrations in mg/m^3 by 6 hours/24 hours, by 5 days/7 days, by the inhalation rate (0.039 m^3/day) of a 0.03 kg mouse and by an absorption factor of 0.5, and by dividing by 0.03 kg. The unadjusted $1/ED_{10}$ of 7.2×10^{-3} $(mg/kg/day)^{-1}$ was derived using the multistage model developed

TABLE 9-4

Derivation of Potency Factor (F) for Methyl Chloride

Reference:	Pavkov et al., 1980, 1981; CIIT, 1983
Exposure route:	inhalation
Species:	mouse
Strain:	B6C3F1
Sex:	male
Vehicle or physical state:	air
Body weight:	0.03 (measured)
Duration of treatment:	24 months
Duration of study:	24 months
Lifespan of animal:	24 months
Target organ:	kidney
Tumor type:	cortical adenomas, adenocarcinomas, papillary cystadenomas and cystadenocarcinomas and tubular cystadenomas
Experimental doses/ exposure:	0, 103, 656, 2065 mg/m^3, 6 hours/day, 5 days/week
Transformed dose (mg/kg/day):	0, 12, 76, 240
Tumor incidence:	0/67, 0/61, 2/57, 22/82
Unadjusted $1/ED_{10}$:	7.2045071×10^{-3} (mg/kg/day)$^{-1}$
Adjusted $1/ED_{10}$ (F factor):	9.5557153×10^{-2} (mg/kg/day)$^{-1}$

by Howe and Crump (1982). The adjusted value (F) of 9.56×10^{-2} $(mg/kg/day)^{-1}$ was calculated by multiplying the unadjusted value by the cube root of the ratio of the reference human body weight (70 kg) to the mouse body weight.

Because the F factor is <1, methyl chloride is placed in Potency Group 4. A Potency Group 4 chemical with a U.S. EPA (1984) classification of Group C, has a LOW hazard ranking according to the revised CAG scheme for reportable quantities under CERCLA.

10. REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. Documentation of the Threshold Limit Values for Substances in Workroom Air. 4th ed. with supplements through 1984. Cincinnati, OH. p. 268-269.

ACGIH (American Conference of Governmental Industrial Hygienists). 1985. TLVs: Threshold Limit Values for Chemical Substances in the Work Environmental. Adopted by ACGIH with intended changes of 1985-1986. Cincinnati, OH. p. 23.

Ahlstrom, R.C., Jr. and J.M. Steele. 1979. Methyl chloride. In: Kirk-Othmer Encyclopedia of Chemical Technology, Vol. 5, 3rd ed. M. Grayson and D. Eckroth, Ed. John Wiley and Sons, Inc., New York. p. 677-685.

Andrews, A.W., E.S. Zawistowski and C.R. Valentine. 1976. A comparison of the mutagenic properties of vinyl chloride and methyl chloride. Mutat. Res. 40: 273-276.

Banerjee, S., P.H. Howard, A.M. Rosenberg, A.E. Dombrowski, H. Surka and D.L. Tudli's. 1984. Development of a general kinetic model for biodegradation and its application to chlorophenols and related compounds. Environ. Sci. Technol. 18: 416-422.

Barassin, J. and J. Combourieu. 1974. Kinetic study of reactions between atomic oxygen and the chlorinated derivates of methane. Bull. Soc. Chim. p. 1-5.

Br'ngmann, G. and R. Kuehn. 1976. Comparative results of the damaging effects of water pollutants against bacteria (Pseudomonas putida) and blue algae (Microcystis aeruginosa). Gas-Wasserfach, Wasser - Abwasser. 117(9): 410-413.

Bringmann, G. and R. Kuehn. 1980. Comparison of the toxicity thresholds of water pollutants to bacteria, algae, and protozoa in the cell multiplication inhibition test. Water Res. 14(3): 231-241.

Brodzinsky, R. and H.B. Singh. 1982. Volatile organic chemicals in the atmosphere: An assessment of available data. Atmospheric Science Center, SRI International, Menlo Park, CA. p. 198. Contract 68-02-3452.

Burmaster, D.E. 1982. The new pollution-groundwater contamination. Environ. 24: 6-13, 33-36.

Bus, J.S. n.d. Personal communication. (Cited in Landry et al., 1983b)

Bus, J.S. 1978. Disposition of carbon-14 methyl chloride in Fischer 344 rats after inhalation exposure. Pharmacol. 20(3): 214.

Bus, J.S., R. Wolkowski-Tyl and C. Barrow. 1982. Alterations in maternal and fetal nonprotein sulfhydryl concentrations in pregnant Fischer 344 rats after acute inhalation exposure to methyl chloride. 20th Annual Meeting of the Teratology Society. June 8-12, 1980. Portsmouth, NH. Teratology. 21(2): 32A.

Butler, R., I.J. Solomon and A. Snelson. 1978. Rate constants for the reaction of OH with halocarbons in the presence of O2 + N2. J. Air Pollut. Control Fed. 28: 1131-1133.

Callahan, M.A., M.W. Slimak, N.W. Gabel, et al. 1979. Water-Related Environmental Fate of 129 Priority Pollutants-Volume II. U.S. EPA, Washington, DC. EPA-440/4-79-029B.

Chapin, R.E., R.D. White, K.T. Morgan and J.S. Bus. 1984. Studies of lesions induced in the testis and epididymis of F-344 rats by inhaled methyl chloride. Toxicol. Appl. Pharmacol. 76(2): 328-343.

CIIT (Chemical Industry Institute of Toxicology). 1983. Final Report on 24-month inhalation study on Methyl Chloride. Prepared by Battelle-Columbus Laboratories, Columbus, OH.

CMR (Chemical Marketing Reporter). 1983. Chemical Profile. Methyl Chloride. March 21. Schnell Publishing Co., Inc., New York. p. 54.

Coleman, W.E., R.D. Lingg, R.G. Melton and F.C. Kopfler. 1976. The occurrence of volatile organics in five drinking water supplies using gas chromatography/mass spectrometry. In: Analysis and Identification of Organic Substances in Water, L. Keith, Ed. Ann Arbor Science Publishers, Ann Arbor, MI. 21: 305-327.

Cox, R.A., R.G. Derwent, A.E.J. Eggleton and J.E. Lovelock. 1976. Photochemical oxidation of halocarbons in the troposphere. Atmos. Environ. 10: 305-308.

Crutzen, P.J. and L.T. Gidel. 1983. A two-dimensional photochemical model of the atmosphere. 2: The tropospheric budgets of the anthropogenic chlorocarbons, carbon monoxide, methane, chloromethane and the effect of various nitrogen oxides (NOX) sources on the tropospheric ozone. J. Geophys. Res. 88: 6641-6661.

Crutzen, P.J., I.S.A. Isaksen and J.R. Mcafee. 1978. The impact of the chlorocarbon industry on the ozone layer. J. Geophys. Res. 83: 345-363.

Davis, D.D., G. Machado, B. Conaway, Y. Oh and R. Watson. 1976. A temperature dependent kinetics study of the reaction of OH with CH_3CL, CH_2CL_2, $CHCL_3$ and CH_3BR. J. Chem. Phys. 65: 1268-1274.

Davis, D.D., W.L. Chameiders and C.S. Kiang. 1982. Measuring atmospheric gases and aerosols. Nature. 295: 186.

Dawson, G.W., A.L. Jennings, D. Drozdowski and E. Rider. 1977. The acute toxicity of 47 industrial chemicals to fresh and saltwater fishes. J. Hazard Mater. 1(4): 303-318.

Derwent, R.G. and A.E.G. Eggleton. 1978. Halocarbon lifetimes and concentration distributions calculated using a two-dimensional tropospheric model. Atmos. Environ. 12: 1261-1269.

Dilling, W.L. 1977. Interphase transfer processes. II. Evaporation rates of chloromethanes, ethanes, ethylenes, propanes, and propylenes from dilute aqueous solutions. Comparisons with theoretical predictions. Environ. Sci. Technol. 11: 405-409.

Dilling, W.L. 1982. Atmospheric environment. Chapter 5. In: Environmental Risk Analysis for Chemicals, R.A. Conway, Ed. Van Nostrand Reinhold Co., New York, NY. p. 154-197.

Dilling, W.L., N.B. Tefertiller and G.J. Kallog. 1975. Evaporation rates and reactivities of methylene chloride, chloroform, 1,1,1-trichloroethane, trichloroethylene, tetrachloroethylene and other chlorinated compounds in dilute aqueous solutions. Environ. Sci. Technol. 9: 833-838.

Dodd, D.E., J.S. Bus and C.S. Barrow. 1982. Nonprotein sulfhydryl alterations in F-344 rats following acute methyl chloride inhalation. Toxicol. Appl. Pharmacol. 62(2): 228-236.

Dunn, R.C. and W.W. Smith. 1947. Acute and chronic toxicity of methyl chloride. IV. Histopathologic observations. Arch. Pathol. 43: 296-300.

Durkin, P.R. 1985. Reference values for risk assessment. Prepared by Syracuse Research Corportion, Syracuse, NY under Contract No. 68-03-3228. ECAO, U.S. EPA, Cincinnati, OH.

Edgerton, S.A., M.A.K. Khalil and R.A. Rasmussen. 1984. Estimates of air pollution from backyard burning. J. Air Pollut. Control Assoc. 34(6): 661-664.

Edwards, P.R., I. Campbell and G.S. Milne. 1982. The impact of chloromethanes on the environment. Part 1. The atmospheric chlorine cycle. Chem. Ind. (London). 16: 574-578.

Evtushenko, G.Y. 1966. No title provided. Gig. Tr. Prof. Zabol. 10: 20. (Russian with English translation) (Cited in U.S. EPA, 1980b)

Evtushenko, G.Y. 1967. Methyl chloride metabolism. Farmakol. Toksikol. (Moscow). 30(2): 239-240. (Russ.) (CA 67:1812m)

Fostel, J., P.F. Allen, E. Bermudez, A.D. Kligerman, J.L. Wilmer and T.R. Skopek. 1985. Assessment of the genotoxic effects of methyl chloride in human lymphoblasts. Mutat. Res. 155(1-2): 75-82.

Gallant, R.W. 1966. Physical properties of hydrocarbons. V. Chlorinated methanes. Hydrocarbon Process. 45: 161-169.

Greenberg, M., R. Anderson, J. Keene, A. Kennedy, G.W. Page and S. Schowgurow. 1982. Empirical test of the association between gross contamination of wells with toxic substances and surrounding land use. Environ. Sci. Technol. 16(1): 14-19.

Guicherit, R. and F.L. Schulting. 1985. The occurrence of organic chemicals in the atmosphere of the Netherlands. Sci. Total Environ. 43(3): 193-219.

Haber, C.L., L.N. Allen, S. Zhao and R.S. Hawson. 1983. Methylotrophic bacteria: Biochemical diversity and genetics. Science. 221: 1147-1153.

Hamm, T.E., Jr., T.H. Raynor, M.C. Phelps, et al. 1985. Reproduction in Fischer-344 rats exposed to methyl chloride by inhalation for two generations. Fundam. Appl. Toxicol. 5(3): P568-77.

Hansch, C. and A.J. Leo. 1979. Substituent Constants for Correlation Analysis in Chemistry and Biology. John Wiley and Sons, Inc., New York. p. 339.

Heppolette, R.L. and R.E. Robertson. 1966. Effect of alpha-methylation on the parameters characterizing hydrolysis in water for a series of halides and bulfonates. Can. J. Chem. 44: 677-684.

Herron, J.T. and R.E. Huie. 1973. Rate constant for the reactions of atomic oxygen (O3P) with organic compounds in the gas phase. J. Phys. Chem. Ref. Data. 2: 467-518.

Holder, J.W. 1984. U.S. EPA Cancer Assessment Group. Memorandum to B. Goldstein, Assistant Administrator for Office of Research and Development. March 9.

Horvath, A.L. 1982. Halogenated Hydrocarbons. Solubility-Miscibility with Water. Marcel Dekker, Inc., New York. p. 889.

Hov, O., S.A. Penkett, I.S.A. Isaksen and A. Semb. 1984. Organic gases in the Norwegian Arctic. Geophys. Res. Lett. 11(5): 425-428.

Howard, C.J. and K.M. Evenson. 1976. Rate constants for the reactions of hydroxyl with methane and fluorine, chlorine and bromine substituted methanes at 296°K. J. Chem. Phys. 64: 197-202.

Howe, R.B. and K.S. Crump. 1982. GLOBAL 82. A computer program to extrapolate quantal animal toxicity data to low doses. Prepared for Office of Carcinogen Standards, OSHA, U.S. Dept. of Labor, Washington, DC. Contract No. 41USC252C3.

Jaber, H.M., W.R. Mabey, A.T. Liu, T.W. Chou and H.L. Johnson. 1984. Data acquisition for environmental transport and fate screening. SRI International, Menlo Park, CA. 312 p. EPA-600/6-84/009. NTIS PB34-243906. NTIS PB84-243955.

Jeong, K.M. and F. Kaufman. 1982. Kinetics of the reaction of hydroxyl radical with methane and with mine Cl- and F-Substituted methanes. 1. Experimental results, comparisons, and applications. J. Phys. Chem. 86: 1808-1815.

Khalil, M.A.K. and R.A. Rasmussen. 1981. Atmospheric methylchloride (CH_3CL). Chemosphere. 10: 1019-1023.

Khalil, M.A.K. and R.A. Rasmussen. 1983. Gaseous tracers of artic haze. Environ. Sci. Technol. 17: 157-164.

Knackmuss, H.J. 1980. Degradation of halogenated and sulfonated hydrocarbons. In: Microbial Degradation of Xenobiotics and Recalcitrant Compounds. FEMS Symposium No. 12. September 15-17. p. 189-212.

Kobayashi, H. and B.E. Rittmann. 1982. Microbial removal of hazardous organic compounds. Environ. Sci. Technol. 16: 170A-182A.

Kool, H.J., C.S. van Kreijl and B.C. Zolteman. 1982. Toxicological assessment of organic compounds in drinking water. Crit. Rev. Environ. Control. 12: 307-357.

Kornbrust, D.J. and J.S. Bus. 1982. Metabolism of methyl chloride to formate in rats. Toxicol. Appl. Pharmacol. 65(1): 135-143.

Kornbrust, D.J. and J.S. Bus. 1983. The role of glutathione and cytochrome P-450 in the metabolism of methyl chloride. Toxicol. Appl. Pharmacol. 67(2): 246-256.

Kornbrust, D.J. J.S. Bus, G. Doerjer and J.A. Swenberg. 1982. Association of inhaled ^{14}C methyl chloride with macromolecules from various rat tissues. Toxicol. Appl. Pharmacol. 65(1): 122-134.

Landry, T.D., T.S. Gushow, P.W. Langvardt, J.M. Wall and M.J. McKenna. 1983a. Pharmacokinetics and metabolism of inhaled methyl chloride in the rat and dog. Toxicol. Appl. Pharmacol. 68(3): 473-486.

Landry, T.D., J.C. Ramsey and M.J. McKenna. 1983b. Pulmonary physiology and inhalation dosimetry in rats: Development of a method and two examples. Toxicol. Appl. Pharmacol. 71(1): 72-83.

Landry, T.D., J.F. Quast, T.S. Gushow and J.L. Mattisson. 1985. Neurotoxicity of methyl chloride in continuously versus intermittently exposed female C57BL/6 Mice. Toxic. Res. Lab., Health and Environ. Sci. U.S.A., Dow Chemical, Midland, MI.

Lioy, P.J., T. Atherholt, J. Bozzelli, et al. 1983. The New Jersey project on airborne toxic elements and organic substances (ATEOS). A summary of the 1981 Summer and 1982 Winter studies. J. Water Pollut. Control Fed. 33: 649-657.

Logan, J.A., M.J. Prather, S.C. Wofsy and M.B. McElroy. 1981. Trophosphric chemistry: A global perspective. J. Geophys. Res. 86: T210-54.

Lovelock, J.E. 1975. Natural halocarbons in the air and in the sea. Nature. 256: 193-194.

Lyman, W.J., W.F. Reehe and D.H. Rosenblatt. 1982. Handbook of Chemical Property Estimation Methods. Environmental Behavior of Organic Compounds. McGraw-Hill Book Co., New York. p. 960.

Mabey, W. and T. Mill. 1978. Critical review of hydrolysis of organic compounds in water under environmental conditions. J. Phys. Chem. Ref. Data. 7: 383-415.

Mitchell, R.I., K. Pavkov, R.M. Everett and D.A. Holzworth. 1979. A 90-day inhalation toxicology study in rats and mice exposed to methyl chloride. Submitted by DuPont De Nemours and Co., Inc. OTS, Washington, DC. OTS No. 878211740, Microfiche No. 205861.

Morgan, K.T., J.A. Swenberg, T.E. Hamm, Jr., R. Wolkowski-Tyle and M. Phelps. 1982. Histopathology of acute toxicity response in rats and mice exposed to methyl chloride by inhalation. Fund. Appl. Toxicol. 2: 293-299.

NAS (National Academy of Sciences). 1978. Chloroform, carbon tetrachloride, and other halomethanes: An environmental assessment. Environmental Studies Board, Commission on Natural Resources, National Research Council, NAS, Washington, DC.

Neely, W.B. 1976. Predicting the flux of organics across the air/water interface. Control Hazard Mater. Spills. Proc. Nat. Conf. 3: 197-200.

NIOSH (National Institute for Occupational Safety and Health). 1984. Carcinogenic Risk Assessment for Occupational Exposure to Monohalomethanes. PB85-111623.

Nolan, R.J., D.L. Rick, T.D. Landry, L.P. McCarty, G.L. Agin and J.H. Saunders. 1985. Pharmacokinetics of inhaled methyl chloride (CH_3CL) in male volunteers. Fundam. Appl. Toxicol. 5(2): P361-9.

Oduntan, D. and O. Odeyemi. 1984. Relative half lives of chloramil and dichlone in different tropical milieux. Environ. Poll. (Ser. A.). 36: 327-335.

OSHA (Occupational Safety and Health Administration). 1985. Permissible Exposure Limits Code of Federal Regulations. 29: 1910.1000.

OTS (Office of Toxic Substances). 1982. Fiche # 205928, OTS, U.S. EPA, Washington, DC.

OTS (Office of Toxic Substances). 1983. Fiche # 206030, OTS, U.S. EPA, Washington, DC.

Otson, R., D.T. Williams and P.D. Bothwell. 1982. Volatile organic compounds in water at thirty Canadian potable water treatment facilities. J. Assoc. Off. Anal. Chem. 65: 1370-1374.

Page, G.W. 1981. Comparison of groundwater and surface water for patterns and levels of contamination by toxic substances. Environ. Sci. Technol. 15(12): 1475-1481.

Palmer, T.Y. 1976. Combustion sources of atmospheric chlorine. Nature (London). 263(5572): 44-46.

Paraskevopoulos, G., D.L. Singleton and R.S. Irwin. 1982. Rates of OH radical reactions. 8. Reactions with CH_2FCl, CHF_2Cl, $CHFCl_2$, CH_3CF_2Cl, CH_3Cl and C_2H_5Cl at 297K. J. Phys. Chem. 85: 561-564.

Patel, R.N., C.T. Hou, A.I. Laskin and A. Felix. 1982. Microbial oxidation of hydrocarbons: Properties of a soluble methane monooxygenase from a facultative methane-utilizing organism, Methylobacterium sp. strain CRL-26. Appl. Environ. Microbiol. 44(5): 1130-1137.

Pavkov, K.L., R.I. Mitchell, W.D. Kerns and M.M. Connell. 1980. 24-Month interim report on a chronic inhalation toxicology study in rats and mice exposed to methyl chloride. Submitted to the Chemical Industry Institute of Toxicology, NC by Battelle Laboratories, Columbus, OH. TSCA Bd. OTS No. 878212060, Microfiche No. 205952.

Pavkov, K.L., R.L. Mitchell and R.L. Persing. 1981. Final Report on a Chronic Inhalation Toxicology Study in Rats and Mice Exposed to methyl Chloride. Submitted to the Chemical Industry Institute of Toxicology, NC by Battelle Laboratories, Columbus, OH. TSCA 8d. OTS No. 878211741, Microfiche No. 205861.

Pearson, C.R. and G. McConnell. 1975. Chlorinated C1 and C2 hydrocarbons in the marine environment. Proc. Roy. Soc. London Ser. 189: 305-332.

Pellizzari, E.D., M.D. Erickson and R.A. Zweidinger. 1979. Formulation of preliminary assessment of halogenated organic compounds in man and environmental media. U.S. EPA, Research Triangle Park, NC. EPA 560/13-79-006. 469 p.

Pellizarri, E.D., T.D. Hartwell, D.S. Harris, R.D. Waddl, D.A. Whitaker and M.D. Erickson. 1982. Purgible organic compounds in mothers' milk. Bull. Environ. Contam. Toxicol. 28: 322-328.

Perry, R.A., R. Atkinson and J.N. Pitts, Jr. 1976. Rate constants for the reaction of hydroxyl radicals with dichlorofluoromethane and chloromethane over the temperature range 298-423°K, and with dichloromethane at 298°K. J. Chem. Phys. 64(4): 1618-1620.

Peto, R., M.C. Pike, N.E. Day, et al. 1980. Guidelines for simple, sensitive significance tests for carcinogenic effects in long-term animal experiments. In: Long-Term and Short-Term Screening Assays for Carcinogens: A Critical Appraisal. WHO, Lyon, France. IARC Monographs, Supplement 2. p. 378.

Putz-Anderson, V., J.V. Setzer, J.S. Croxton and F.C. Phipps. 1981a. Methyl chloride and diazepam effects on performance. Scand. J. Work Environ. Health. 7: 8-13.

Putz-Anderson, V., J.V. Setzer and J.S. Croxton. 1981b. Effects of alcohol, caffeine and methyl chloride on man. Psychol. Rep. 48(3): 715-725.

Rasmussen, R.A., L.E. Rasmussen, M.A.K. Khalil and R.W. Dalluge. 1980. Concentration distribution of methyl chloride in the atmosphere. J. Geophys. Res. 85: 7350-7356.

Rasmussen, R.A., M.A.K. Khalil and R.W. Dalluge. 1981. Atmospheric trace gases in Antarctica. Science. 211: 285-287.

Rasmussen, R.A., M.A.K. Khalil and J.S. Chang. 1982. Atmospheric trace gases over China. Environ. Sci. Technol. 16: 124-126.

Redford-Ellis, M. and A.H. Gowenlock. 1971a. Reaction of chloromethane with human blood. Acta Pharmacol. Toxicol. 30(1-2): 36-48.

Redford-Ellis, M. and A.H. Gowenlock. 1971b. Reaction of chloromethane with preparations of liver, brain, and kidney. Acta Pharmacol. Toxicol. 30(1-2): 49-58.

Repko, J.D. 1981. Neurotoxicity of methyl chloride. Neurobehav. Toxicol. Teratol. 3(4): 425-429.

Repko, J.D. and S.M. Lasley. 1979. Behavioral, neurological, and toxic effects of methyl chloride: A review of the literature. CRC Crit. Rev. Toxicol. 6(4): 283-302.

Repko, J.D., P.D. Jones, L.S. Garcia, Jr., E.J. Schneider, E. Roseman and C.R. Corum. 1976. Behavioral and neurological effects of methyl chloride. Behavioral and neurological evaluation of workers exposed to industrial solvents: Methyl chloride. DHEW (NIOSH) Publ. (U.S.); 77-125: 199.

Robbins, D.E. 1976. Photodissociation of methyl chloride and methyl bromide in the atmosphere. Geophys. Res. Lett. 3: 213-216.

Sabel, G.V. and T.P. Clark. 1984. Volatile organic compounds as indicators of municipal solid waste leachate contamination. Waste Manag. Res. 2: 119-130.

Sanhueza, E. and J. Heicklen. 1975. Chlorine-atom sensitized oxidation of dichloromethane and chloromethane. J. Phys. Chem. 79: 7-11.

Simmon, V.F. 1978. Structural correlations of carcinogenic and mutagenic alkyl halides. Struct. Correl. Carcinog. Mutagen. p. 163-171. DHEW Publ. (FDA) (U.S.); ISS FDA 78-1046.

Simmon, V.F. 1981. Applications of the Salmonella/microsome assay. Short-term tests. Chem. Carcinog. p. 120-126.

Simmon, V.F., K. Kauhanen and R.G. Tardiff. 1977. Mutagenic activity of chemicals identified in drinking water. Dev. Toxicol. Environ. Sci. 2: 249-258.

Singh, H.B., L.J. Salas, H. Shigeisi, A.J. Smith, E. Scribner and L.A. Cavanagh. 1979. Atmospheric districutions, sources and sinks of selected halocarbon, hydrocarbons, SF6 + N2O. U.S. EPA, Research Triangle Park, NC. EPA 600/3-79-107. p. 134.

Singh, H.B., L.J. Salas and H. Shigeisi. 1981. Measurements of some potentially hazardous organic chemicals in urban environments. Atmos. Environ. 15: 601-612.

Singh, H.B., L.J. Salas and R.E. Stiles. 1982. Distribution of selected gaseous organic mutagens and suspect carcinogens in ambient air. Environ. Sci. Technol. 16: 872-880.

Smith, W.W. 1947. The acute and chronic toxicity of methyl chloride. III. Hematology and biochemical studies. J. Ind. Hyg. Toxicol. 29: 185-189.

Smith, W.W. and W.F. von Oettingen. 1947a. The acute and chronic toxicity of methyl chloride. I. Mortality resulting from exposure to methyl chloride in concentrations of 4000 to 300 parts per million. J. Ind. Hyg. Toxicol. 29: 47-52.

Smith, W.W. and W.F. von Oettingen. 1947b. Symptomatology of animals poisoned by methyl chloride. The acutenol chronic toxicity of methyl chloride. II. J. Ind. Hyg. Toxicol. 29: 123-128.

Spence, J.W., P.L. Hanst and B.W. Gay, Jr. 1976. Atmospheric oxidation of methyl chloride, methylene chloride and chloroform. J. Air. Pollut. Control Assoc. 76: 994-996.

Sperling, F., F.J. Macri and W.F. von Oettingen. 1950. Arch. Ind. Hyg. Occup. Med. 1: 215-224.

SRI (Stanford Research Institute). 1985. 1985 Directory of Chemical Producers. United States of America. SRI International, Menlo Park, CA. p. 714.

Staples, C.A., A. Werner and T. Hoogheem. 1985. Assessment of priority pollutant concentrations in the United States using STORET Database. Environ. Toxicol. Chem. 4: 131-142.

U.S. EPA. 1975. Preliminary Assessment of Suspected Carcinogens in Drinking Water. Interim Report to Congress, June, 1975. Washington, DC.

U.S. EPA. 1977. Computer print-out of non-confidential production data from TSCA inventory. OPTS, CID, U.S. EPA, Washington, DC.

U.S. EPA. 1980a. Ambient Water Quality Criteria for Halomethanes. U.S. EPA, Washington, DC. EPA 440/5-80-051.

U.S. EPA. 1980b. TSCA Chemical Assessment Series. Assessment of Testing Needs: Chloromethane. U.S. EPA, Washington, DC. p. 84. EPA 560/11-80-015.

U.S. EPA. 1980c. Guidelines and methodology for the preparation of health effect assessment chapters of the ambient water quality criteria documents. ECAO, OHEA, ORD, U.S. EPA, Cincinnati, Oh.

U.S. EPA. 1982. Errata: Halomethanes. Ambient Water Quality Criterion for the Protection of Human Health. Environmental Criteria and Assessment Office, U.S. EPA, Cincinnati, OH. ECAO-CIN-0023.

U.S. EPA. 1983. Reportable Quantity Document for Methyl Chloride. ECAO, Cincinnati, OH.

U.S. EPA. 1984a. Proposed Guidelines for Carcinogen Risk Assessment. U.S. EPA, Washington, DC. Federal Register. 49(227):46294-46301.

U.S. EPA. 1984b. TSCA Preregulatory Assessment of Chloromethane. U.S. EPA, Washington, DC. May 1984 Draft.

U.S. EPA. 1985. Summary for Acceptable Daily Intakes (ADIs) for Oral Exposure. ECAO-CIN-432. Revised May, 1985. ECAO, U.S. EPA, Cincinnati, OH.

USITC (U.S. International Trade Commission). 1985. Synthetic Organic Chemicals. U.S. Production and Sales, 1984. USITC Publ. 1745, Washington, DC. p. 285.

Van Doorn, R., P.JA. Borm, C.M. Leijdekkers, P.T. Henderson, J. Reuvers and T.J. Van Bergen. 1980. Detection and identification of S-methylcysteine in urine of workers exposed to methyl chloride. Int. Arch. Occup. Environ. Health. 46(2): 99-110.

von Oettingen, W.F., C.C. Powell and N.E. Sharpless. 1950. Comparative studies of the toxicity and pharmacodynamic action of chlorinated methones with special reference to thei: physical and chemical characteristics. Arch. Int. Pharmacodyn. LXXXS. 1: 17-34.

Weast, R.C. 1980. CRC Handbook of Chemistry and Physics. CRC Press, Inc., Boca Raton, FL. p. c-410.

Wolkowski-Tyl, R., M. Phelps and J.K. Davis. 1983a. Structural teratogenicity evaluation of methyl chloride in rats and mice after inhalation exposure. Teratology. 27(2): 181-196.

Wolkowski-Tyl, R., A.D. Lawton, M. Phelps and T.E. Hamm, Jr. 1983b. Evaluation of heart malformations in B6C3F1 mouse fetuses induced by in utero exposure to methyl chloride. Teratology 27(2): 197-206.

Working, P.K., J.S. Bus and T.E. Hamm, Jr. 1985a. Reproductive effects of inhaled methyl chloride in the male Fischer-344 rat. I. Mating performance and dominant lethal assay. Toxicol. Appl. Pharmacol. 77(1): 133-143.

Working, P.K., J.S. Bus and T.E. Hamm. 1985b. Reproductive effects of inhaled methyl chloride in the male Fischer 344 rat. II. Spermatogonial toxicity and sperm quality. Toxicol. Appl. Pharmacol. 77: 144-157.

Yung, Y.L., M.B. McElroy and S.C. Wofsy. 1975. Atmospheric halocarbons: A discussion with emphasis on chloroform. Geophys. Res. Lett. 2: 397-399.

APPENDIX

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of the following:

CASR online (U.S. EPA Chemical Activities Status Report)
CAS online STN Internation
TOXLINE
TOXBACK 76
TOXBACK 65
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP
NTIS
Federal Register

These searches were conducted in October, 1985. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. Documentation of the Threshold Limit Values, 4th ed. (Includes Supplemental Documentation through 1984). Cincinnati, OH. 405 p.

ACGIH (American Conference of Governmental Industrial Hygienists). 1985. TLVs: Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1985-1986. Cincinnati, OH. 114 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2A. John Wiley and Sons, NY. p. 2878.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2B. John Wiley and Sons, NY. p. 2879-3816.

Clayton, G.D. and F.E. Clayton, Ed. 1982. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2C. John Wiley and Sons, NY. p. 3817-5112.

Grayson, M. and D. Eckroth, Ed. 1978-1984. Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed. John Wiley and Sons, NY. 24 Volumes and Supplement.

Hamilton, A. and H.L. Hardy. 1974. Industrial Toxicology, 3rd ed. Publishing Sciences Group, Inc., Littleton, MA. 575 p.

IARC (International Agency for Research on Cancer). IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. WHO, IARC, Lyons, France.

ITII (International Technology Information Institute). 1982. Toxic and Hazardous Industrial Chemicals Safety Manual for Handling and Disposal with Toxicity and Hazard Data. ITII, Tokyo, Japan. 700 p.

NTP (National Toxicology Program). 1985. Toxicology Research and Testing Program. Chemicals on Standard Protocol. Management Status.

Ouellette, R.P. and J.A. King. 1977. Chemical Week Pesticide Register. McGraw-Hill Book Co., NY.

Sax, I.N. 1984. Dangerous Properties of Industrial Materials, 6th ed. Van Nostrand Reinhold Co., NY.

SRI (Stanford Research Institute). 1985. Directory of Chemical Producers. Menlo Park, CA.

U.S. EPA. 1985. Status Report on Rebuttable Presumption Against Registration (RPAR) or Special Review Process. Registration Standards and the Data Call in Programs. Office of Pesticide Programs, Washington, DC.

U.S. EPA. 1985. CSB Existing Chemical Assessment Tracking System. Name and CAS Number Ordered Indexes. Office of Toxic Substances, Washington, DC.

USITC (U.S. International Trade Commission). 1983. Synthetic Organic Chemicals. U.S. Production and Sales, 1982, USITC Publ. 1422. Washington, DC.

Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Co., NY.

Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

Windholz, M., Ed. 1983. The Merck Index, 10th ed. Merck and Co., Inc., Rahway, NJ.

In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

Battelle's Columbus Laboratories. 1971. Water Quality Criteria Data Book. Volume 3. Effects of Chemicals on Aquatic Life. Selected Data from the Literature through 1968. Prepared for the U.S. EPA under contract No. 68-01-0007. Washington, DC.

Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. Summaries of Toxicity Tests Conducted at Columbia National Fisheries Research Laboratory. 1965-1978. U.S. Dept. Interior, Fish and Wildlife Service. Resource Publ. 137. Washington, DC.

McKee, J.E. and H.W. Wolf. 1963. Water Quality Criteria, 2nd ed. Prepared for the Resources Agency of California. State Water Quality Control Board. Publ. No. 3-A.

Pimental, D. 1971. Ecological Effect of Pesticides on Non-Target Species. PB-269605. Prepared for the U.S. EPA, Washington, DC.

Schneider, B.A. 1979. Toxicology Handbook. Mammalian and Aquatic Data. Book 1: Toxicology Data. EPA 540/9-79-003. NTIS PB 80-196876. Office of Pesticide Programs, U.S. EPA, Washington, DC.